이학박사학위논문

Metal-Vinylidene-Catalyzed Oxidative Functionalization of Terminal Alkynes

and

Synthetic Studies toward (+)-Fendleridine

금속 비닐리덴 매개 말단 알카인의 산화적 기능화 촉매반응 및 (+)-펜들러리딘 합성 연구

2019 년 8 월

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ABSTRACT

Described in this dissertation are development and application of the catalysis mediated by transition metal vinylidene complexes. With a brief survey of oxidative functionalization of metal vinylidene species (Chapter 1), a mechanistically distinct approach toward oxygenative [2 + 2] cycloaddition of terminal alkynes with imines is discussed. It has been revealed that oxidative functionalization of terminal alkynes has a diverse mechanistic modalities depending on both metal complexes and oxidants employed. Through the studies, we have discovered diverse facets of the metal-vinylidene-catalyzed oxidative functionalization of terminal alkynes, in which terminal alkynes are converted to an array of acyl donors in practical and general senses (Chapter 2). Parallel with the effort in the new reaction discovery, an application of metal vinylidene catalysis has been pursued in the context of complex total synthesis. A cascade cyclization approach to (+)-fendleridine has been devised taking advantage of *anti*-Markovnikov selectivity in the metal-vinylidene-catalyzed cyclization of terminal alkynes. During the research, the oxidative indole acylation and relay-acyl-migration reactions were established. In addition, the feasibility of each cyclization event was briefly investigated. Details of the synthetic studies toward (+)-fendleridine are discussed in Chapter 3.

Keywords: Metal Vinylidene, Oxidative Functionalization, Catalysis, Total Synthesis, (+)-Fendleridine

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Table of Contents

List of Schemes

List of Figures

List of Tables

Table 2.13. Iterative Amidation Reaction for β-Peptide Synthesis

List of Abbreviations

Ac	acetyl
Ar	aryl
aq.	Aqueous
atm	atmosphere
Boc	*ter*t-butyloxycarbonyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
cat.	catalytic
cod	cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine

DMF	*N*,*N*-dimethylformamide
DPA	diphenylacetyl
dppf	1,1’-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
Et	ethyl
EtOAc	ethyl acetate
Me	methyl
MeCN	acetonitrile
Mes	mesityl
MS	molecular sieve
NCS	*N*-chlorosuccinimide
Ph	phenyl
Phth	phthalyl
PMP	*para*-methoxyphenyl
PNP	*para*-nitrophenyl
Pr	propyl
pyr	pyridine
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl

TES	triethylsilyl
Tf	trifluoromethylsulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TES	triethylsilyl
TMS	trimethylsilyl
Tp	tris(pyrazolyl)borate
Troc	2,2,2-trichloroethyloxycarbonyl
Ts	*p*-toluenesulfonyl

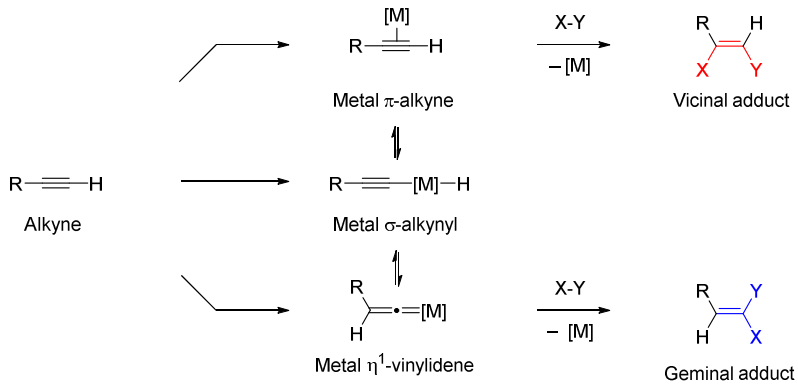
Chapter 1. Oxidation of Metal Vinylidene Complexes

1.1. Introduction

Transition metal catalysis has provided a number of powerful tools in organic synthesis. With the advent of new mechanistic modalities, selective functionalization of specific chemical bonds becomes possible, leading to development of conceptually new reactions that are otherwise infeasible or difficult to implement. Among various substrates that can selectively activated with transition metals, alkynes are an attractive target for new reaction development. While being stable under numerous reaction conditions, alkynes can be activated upon coordination to a transition metal, which may be further harnessed for catalysis. In a chemoselectivity perspective, a number of transition metal complexes with high-alkyne-affinity are available, providing great opportunities for alkynes to be strategically employed in organic synthesis without complication by the issue of functional group tolerance.

Organometallic species derived from alkynes, such as metal π–alkyne, σ–alkynyl, and vinylidene complexes, exist in dynamic equilibrium with one another. A notable aspect of this equilibrium is that each complex has a distinct mode of reactivity. In general, the addition to metal vinylidene complexes brings about formation of a 1,1–geminal adduct, whereas 1,2–vicinal addition is the prevalent mode for metal π–alkyne complexes (Scheme 1.1). Consequently, the hydrofunctionalization reaction (cf. X = H) effected through

metal vinylidene species results in *anti*-Markovnikov addition to terminal alkynes.[1-4]



Scheme 1.1. Organometallic Complexes Derived from Terminal Alkynes

This unique reactivity of metal vinylidene complexes can be explained by the molecular orbital theory (Figure 1.1).[5,6] A metal-free vinylidene has an empty *p*–orbital perpendicular to the C–C π–bond, which readily engages in addition reaction with nucleophiles. The strong electrophilicity of organic vinylidenes is translated into that of metal-complexed vinylidenes, although electrophilicity of the vinylidene center is largely mitigated upon complexation with a transition metal. Nonetheless, the lowest-energy molecular orbital (LUMO) of the metal vinylidene is yet localized on the vinylidene center. It is this electronic feature that makes nucleophilic addition onto the vinylidene center the most dominant reaction pathway of metal vinylidene species, while various modes

of pericyclic reactions involving C=C and C=M double bonds have also been realized.[4,7]

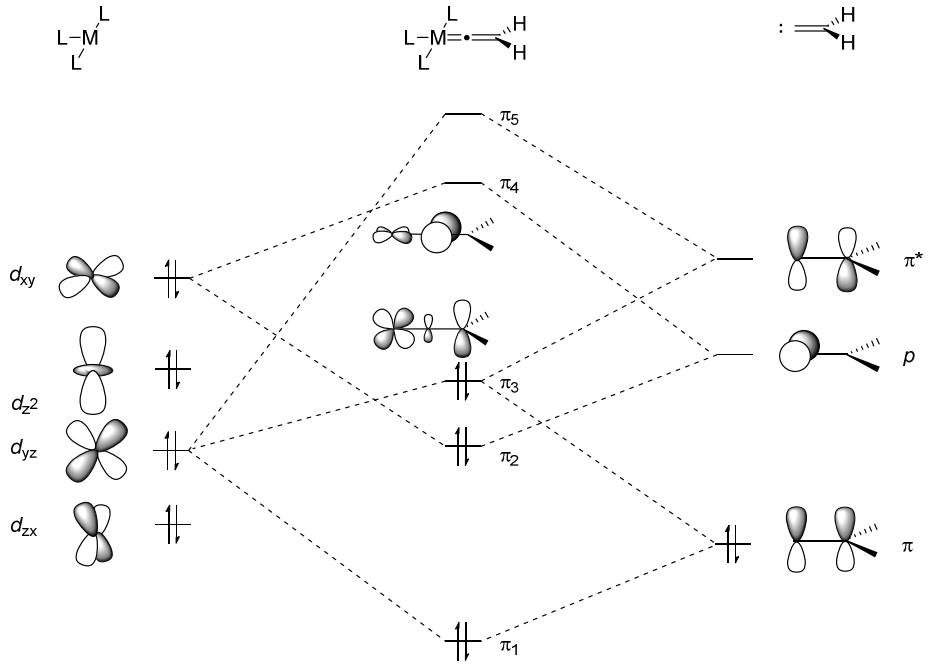


Figure 1.1. Simplified depiction of Frontier Molecular Orbitals (FMO) of a d^8–metal vinylidene. Orbitals corresponding to σ–bonds are omitted for clarity.

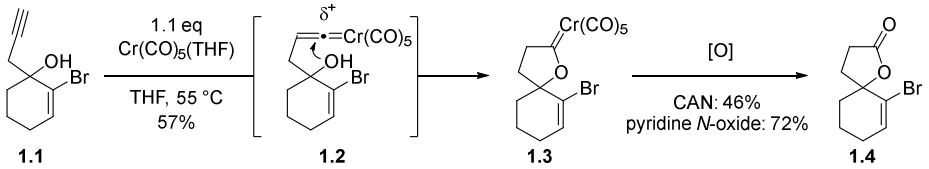
Among a variety of nucleophiles employed in metal vinylidene chemistry, certain types of heteroatom nucleophiles can induce not only an addition reaction, but also a redox reaction at the vinylidene center. Nucleophiles in line with this reactivity often possess a heteroatom–heteroatom bond, which can transfer one heteroatom to the vinylidene center, giving rise to a post-vinylidene intermediate of a higher oxidation state. The oxidation of metal vinylidene

complexes shall confer more dimensions to the metal-vinylidene-catalysis, as it engenders new reactive organometallic species such as metallo-ketenes or acylmetal complexes. The rest of this chapter will cover stoichiometric- and catalytic precedents in the field of oxidative transformation of alkynes mediated by a metal vinylidene in order to introduce fundamental reactivity of metal vinylidene toward the redox process.

1.2. Oxidation of Fischer Carbenes Derived from Metal Vinylidene

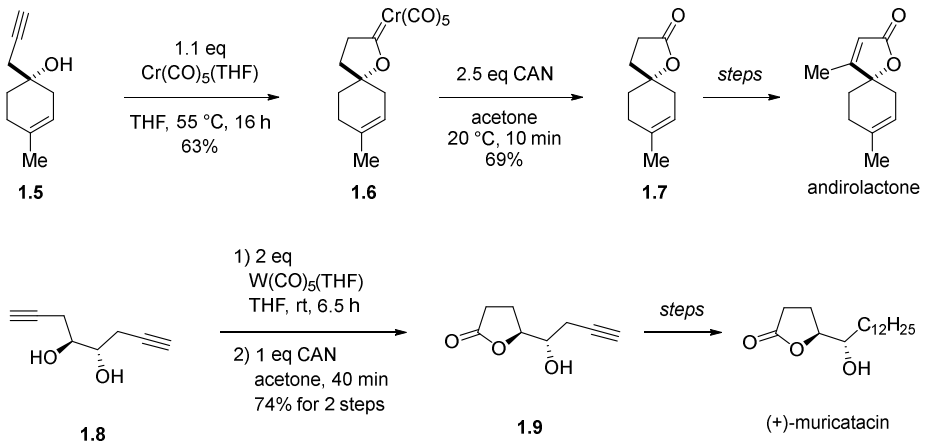
1.2.1. Stoichiometric Reactions

The oxidative addition process can be divided into two subclasses depending on the preceding elementary step. When the addition reaction occurs prior to oxidation, Fisher carbene is generated and poised for oxidation. For example, nucleophilic addition of the pendent alcohol to chromium vinylidene **1.2**, generated from alkynol **1.1** and a pentacarbonylchromium complex, gave rise to Fisher carbene **1.3** (Scheme 1.2). Oxidation of the resulting Fischer carbene was shown to be feasible using ceric ammonium nitrate (CAN) or pyridine *N*-oxide, affording the oxidative addition product **1.4**.[8]

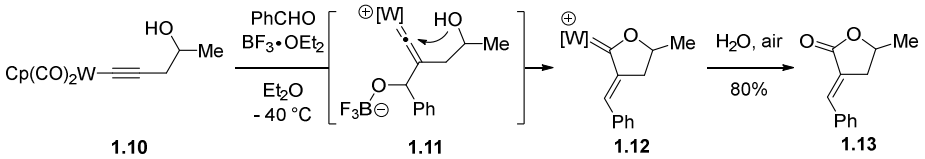


Scheme 1.2. Oxidative Cyclization of an Alkynol via Fischer Carbene

The Quayle group utilized this oxidative cyclization process for the syntheses of lactone natural products, such as andirolactone and (+)–muricatacin (Scheme 1.3).[9,10] While the pentacarbonylchromium complex was the stoichiometric mediator for the oxidative cyclization of alkynol **1.5** en route to andirolactone, a tungsten analog was also shown to be competent for the same transformation. In this case, γ-butyrolactone **1.9** was preferentially formed from symmetric diol **1.8**, rather than a six-membered lactone. It is also worthy of note that unlike the oxidative cyclization where two equivalents of tungsten were necessary, the same tungsten complex could be exploited catalytically for "non-oxidative" cycloisomerization.[11]

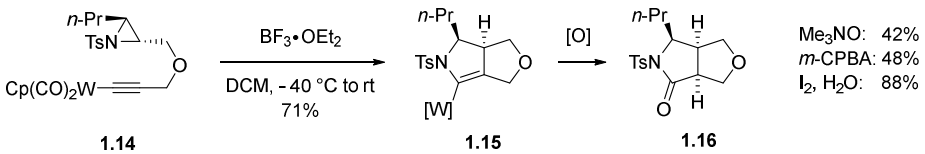


Scheme 1.3. Quayle's Synthesis of Andirolactone and (+)–Muricatacin



Scheme 1.4. Oxidation of a Cp-Ligated Tungsten Fischer Carbene

In 1997, Liu and coworkers reported formation of vinylidene complexes from carbonyl addition of a preformed alkynyltungsten species. Fischer carbene **1.12** was generated from intramolecular capture of tungsten vinylidene **1.11**, and subsequent oxidative hydrolysis by exposure to air and water produced lactone **1.13** (Scheme 1.4).[12-14]



Scheme 1.5. Oxidation of a Cp-Ligated Alkenyltungsten

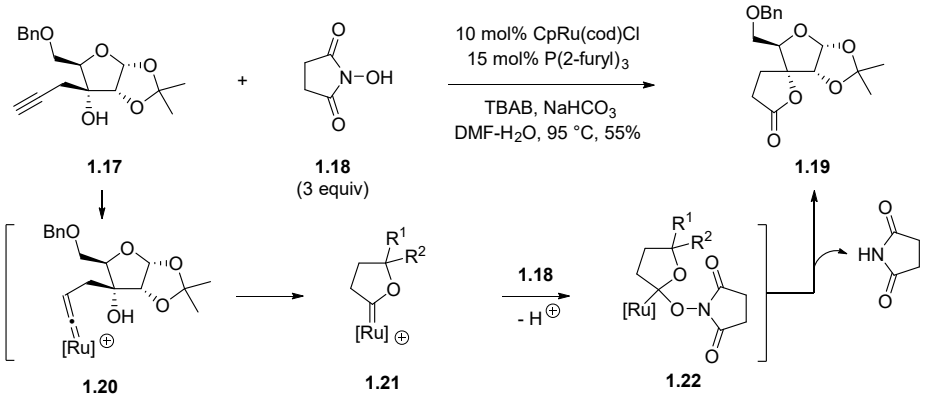
While prevalent intermediates in the addition-oxidation sequence are Fischer carbenes, an alkenylmetal complex has also been reported as an intermediate for oxidative cyclization. In a similar way to Scheme 1.4, aziridine **1.14** underwent alkylative vinylidene formation (cf. **1.11**), followed by addition of the sulfonamide group leading to alkenyltungsten **1.15**. On subsequent oxidation, alkenyltungsten **1.15**, or its tautomeric Fischer carbene form, is

proposed to afford bicyclic lactam **1.16** (Scheme 1.5).[15] A number of oxidative functionalization reactions through tungsten vinylidenes and/or tungsten Fisher carbenes have been developed using various electrophiles such as acetals,[16] oxiranes,[17,18] and azacarbenium.[19]

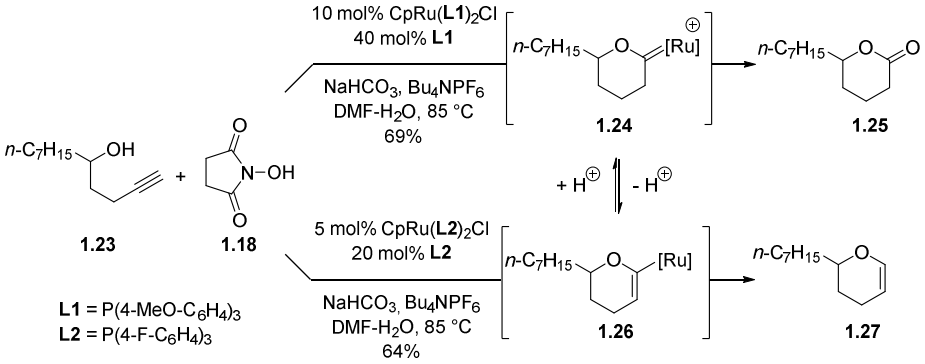
1.2.2. Catalytic Reactions

Use of strong oxidants, which are often incompatible with transition metal catalysts, hampers evolution of aforementioned stoichiometric reactions to their catalytic processes. While dimethyl sulfoxide (DMSO) was noted to oxidize a Fischer carbene complex,[20] sulfide byproduct may become a risk as it can poison the catalytic system.

In 1999, Trost and Rhee reported the first catalytic process enabling oxidative cyclization of alkynols in an intramolecular setting (Scheme 1.6).[21] In this ruthenium-catalyzed process, *N*–hydroxysuccinimide (**1.18**) was adopted as the metal-compatible oxidant. It is proposed that nucleophilic attack of intramolecular alcohol to the vinylidene center of **1.20** gives Fischer carbene **1.21**, which then undergoes sequence of addition of *N*–hydroxysuccinimide and *N*–*O* bond cleavage, providing γ–butyrolactone **1.19**.



Scheme 1.6. Ruthenium-Catalyzed Oxidative Cyclization of Alkynols



Scheme 1.7. Oxidative Cyclization of Alkynols for 6-Membered Oxacycles

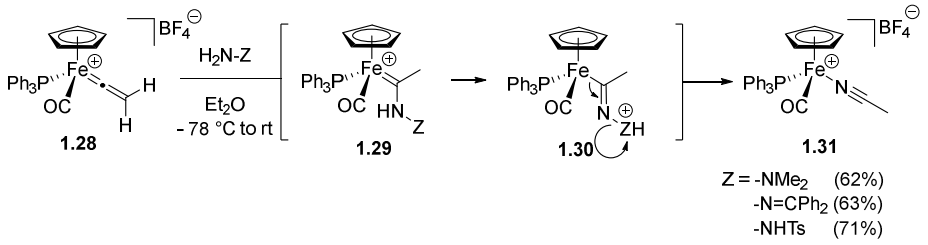
Using a homologated system for the synthesis of δ–lactone, Trost and Rhee observed a mechanistic divergence (Scheme 1.7).[22] With complexation by an electron-rich phosphine ligand, ruthenium Fischer carbene **1.24** is proposed to be a dominant intermediate, resulting in δ–lactone **1.25** in an analogous manner to Scheme 1.6. In contrast, electron-deficient ligand **L2** reorients the selectivity toward the non-oxidative cyclization, giving rise to cyclic enol **1.27**. It is

suggested that the α–deprotonation of Fischer carbene **1.24** is facilitated by reduced electron-density of the ruthenium center, forcing the equilibrium to be shifted toward alkenylruthenium **1.26** and affording the cycloisomerization product **1.27**.

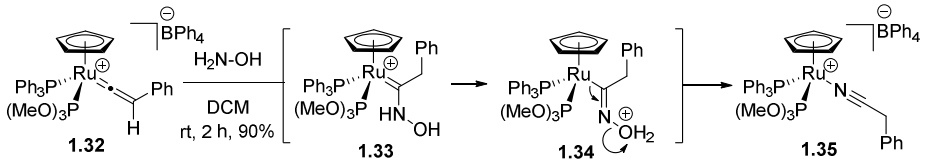
1.3. Atom-Transfer Reactions of Metal Vinylidene

1.3.1. Stoichiometric Reactions

Oxidation of pre-formed Fisher carbene complexes has witnessed noticeable success by using oxidants with a heteroatom–heteroatom bond.[8,23-25] The innate nucleophilicity of these organic oxidants is sufficient to attack the vinylidene center. For example, Barrett et al. reported the synthesis of an iron acetonitrile complex from iron vinylidene **1.28**, using hydrazine derivatives as nucleophilic oxidants (Scheme 1.8).[26] The addition of dimethylhydrazine, benzophenone hydrazone, or *p*–tosylhydrazide to the vinylidene center of **1.28** is suggested to furnish amino–Fischer carbene **1.29**. Subsequent tautomerization, proton shuttling, and *N–N* bond cleavage afforded acetonitrile complexes **1.31** in good yield, in which the carbon atom of acetonitrile was derived from oxidation of the vinylidene α–carbon by hydrazine derivatives.



Scheme 1.8. Nitrogen-Transfer to an Iron Vinylidene Using Hydrazines



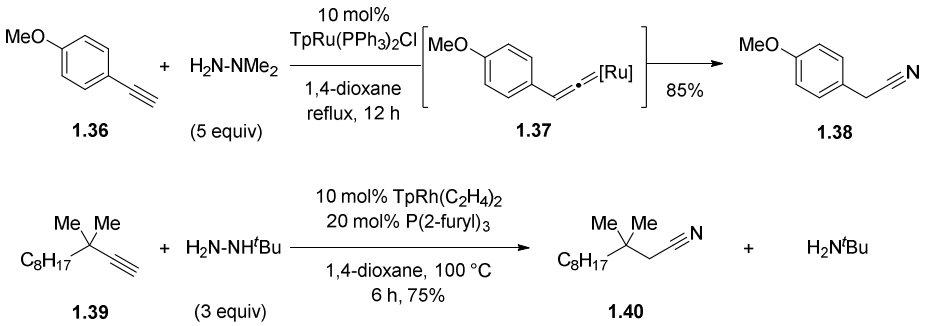
Scheme 1.9. Nitrogen-Transfer to a Ruthenium Vinylidene Using Hydroxylamine

In addition to hydrazines, a hydroxylamine can also be added to a Cp–Ru complex in a similar manner, affording ruthenium nitrile complex **1.35** (Scheme 1.9).[27] In this case, cleavage of the *N–O* bond is responsible for oxidation of the vinylidene center of **1.32**, liberating water as a byproduct. The use of hydrazines was also reported to produce the same ruthenium nitrile complex.

1.3.2. Catalytic Reactions

Oxidative addition reactions, making use of hydrazines and hydroxylamines as atom-transfer reagents, have been translated into a catalytic version during the

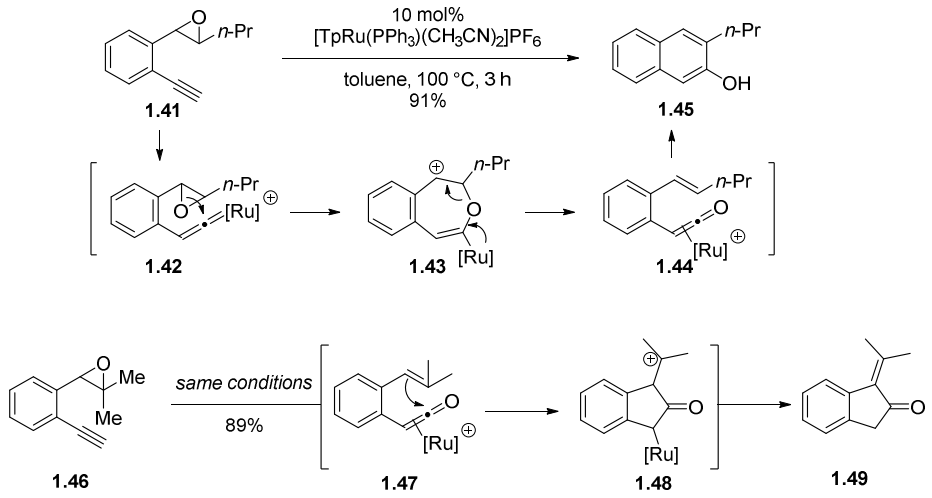
last two decades. In 2002, Fukumoto and coworkers reported that a Tp–Ru complex was an efficient catalyst for converting alkyne **1.36** to nitrile **1.38** with proposed intermediacy of ruthenium vinylidene **1.37** (Scheme 1.10).[28] In cases of sterically-demanding substrates such as **1.39**, a Tp–Rh catalyst was more effective using *t*–butylhydrazine as a nitrogen-transfer reagent.[29]



Scheme 1.10. Catalytic Nitrogen-Transfer to Terminal Alkynes

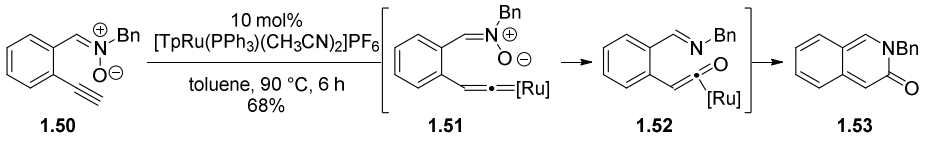
The atom-transfer reactions of metal vinylidenes, effecting nucleophilic addition with concomitant oxidation, have been further developed to include oxygen atom-transfer. The Liu group reported that intramolecular oxygen-transfer was feasible from ethynylepoxide **1.41** (Scheme 1.11).[30-32] In the presence of a cationic Tp–Ru catalyst, ruthenium vinylidene **1.42**, derived from alkynyl epoxide **1.41**, received an oxygen atom from the proximal epoxide, generating metallo-ketene intermediate **1.44**. Regio-divergency was noted in the subsequent reactions of this metallo-ketene intermediate. While naphthol **1.45** is likely to be a consequence of 6π–electrocyclization of metallo-ketene

1.44, cationic π–cyclization may lead to 2-indanone **1.49**. Substantial stability of tertiary carbocation **1.48** presumably renders the cationic π–cyclization pathway more viable in the latter case.



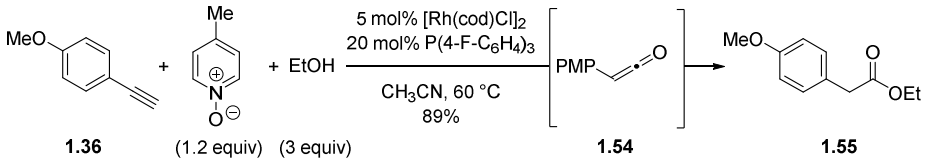
Scheme 1.11. Catalytic Oxygen-Transfer Reaction of Ethynylepoxides

As shown in a number of stoichiometric precedents, the cleavage of an *N–O* bond can be used as an oxygen-transfer motif. In 2009, nitrone was revealed to be compatible with transition-metal-vinylidene-mediated catalysis by Liu and Pati. A mechanistic similarity lies between epoxide and nitrone, as is shown by intramolecular oxygen-transfer with ruthenium vinylidene **1.51** that gave rise to metallo-ketene **1.52**. Again, 6π–electrocyclization is the likely pathway that affords isoquinolone **1.53** from the metallo-ketene (Scheme 1.12).[33]



Scheme 1.12. Catalytic Oxygen-Transfer Reaction of Nitrones

In a viewpoint of structural change effected by the oxygen-transfer reaction, terminal alkyne can be regarded as an acyl group, a ubiquitous polar functionality. On the basis of availability of terminal alkynes and drastic change of polarity, alkyne-to-acyl transformation shall become a promising acylation tool. However, the intramolecular oxygen-transfer reaction require pre-setting of requisite moieties, limiting its application.



Scheme 1.13. Intermolecular Oxygenative Addition to Terminal Alkynes

An intermolecular alkyne-to-acyl transformation has been recently realized. In 2013, Lee and Kim reported for the first time that pyridine *N*-oxide derivatives participate catalytically in oxygenation of a rhodium vinylidene species. Among an array of *N*-oxide derivatives tested, 4-picoline *N*-oxide gave the best result with which terminal alkyne **1.36** gave rise to ester **1.55** using ethanol as an acyl-capturing nucleophile. The putative ketene intermediate **1.54**,

generated from oxygen-transfer to a rhodium vinylidene, underwent addition reactions with a variety of nucleophiles furnishing carboxylic acids, carboxamides, and ester derivatives (Scheme 1.13).[34]

1.4. Conclusion and Outlook

The evolution of oxidative addition to alkynes via metal vinylidene species provides a new synthon for the synthetic community, making it possible to regard terminal alkynes as ketene- and/or acyl-surrogates. Especially, the ketene-generating oxygenation reaction developed by Lee and Kim paved a way to connect vinylidene and ketene chemistry. Indeed, applications of the catalytic metallo-ketene generation have been followed by approaches taking advantage of the reactivity of the ketene intermediate, such as tandem addition/aldol condensation,[35] macrolactonization,[36] electrocyclization,[37] and cycloaddition reactions.[38] On the other hand, Fischer carbene oxidation has potentials to be further developed to intermolecular reactions, which provide general and controllable means for acylation reactions. However, while catalytic generation of the ketene intermediate has been realized by oxidation of metal vinylidene complexes, catalytic Fisher carbene oxidation chemistry has remained undeveloped. On the basis of this background, we have endeavored to utilize ketene chemistry and to improve Fisher carbene oxidation chemistry, which is described in Chapter 2.

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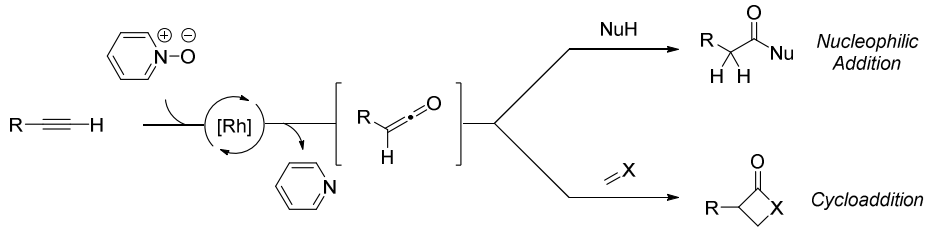
Chapter 2. Oxygenative Functionalization of Terminal Alkynes via Metal-Vinylidene-Mediated Catalysis

2.1. Oxygenative [2 + 2] Cycloaddition Reaction of Terminal Alkynes with Imines

2.1.1. Introduction

In a vantage point of α–functionalization of metal vinylidenes, oxidation of terminal alkynes through a metallo-ketene intermediate is a powerful tool for construction of multiple chemical bonds, in which two carbon–heteroatom σ–bonds and one π–bond are emanating from single catalysis (cf. Scheme 1.13). However, the resultant addition products lack diversity on the β–position possessing only two C–H bonds, one of which is originated from the alkynyl C–H bond and the another from nucleophiles (Scheme 2.1). This imbalance of degree of functionalization at the two carbon atoms is a general problem in metal vinylidene chemistry; among 400 references covered by a recent review, only 7% of them, 27 references, dealt with β–functionalization.[1] Thus, functionalization of the β–carbon of alkynes, especially those of making synthetically valuable C–C bonds, is highly desirable.



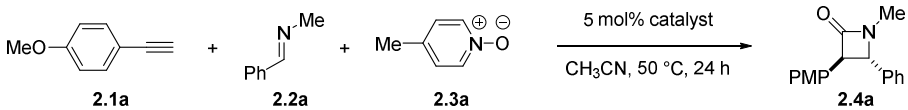
Scheme 2.1. Oxygenative Addition and -Cycloaddition Processes

We envisioned that the metallo-ketene intermediate can further benefit from a classic reactivity of ketenes, engendering C–C bond formation through [2 + 2] cycloaddition. In particular, this [2 + 2] cycloaddition includes imines as a reaction partner, affording synthetically and biologically valuable β–lactam motifs.[2-5] Described herein is our pursuit toward multiple bond formations by single vinylidene-catalysis, using the [2 + 2] cycloaddition reactivity of ketenes.

2.1.2. Reaction Optimization

Through our efforts directed toward development of new reactions making use of a metallo-ketene intermediate, an oxygenative [2 + 2] cycloaddition of alkynes with imines has been realized. In the discovery stage, an initial hit was found with the original reaction conditions for oxygenative addition,[6] which gave β–lactam **2.4a** in 90% yield from terminal alkyne **2.1a** and imine **2.2a** (Table 2.1, entry 1). Catalyst screening studies encompassing an array of rhodium(I) and ruthenium(II) complexes showed the commercial Wilkinson's catalyst, as well as other 1:2 rhodium(I)/phosphine systems, to be efficient in

providing β–lactam products with exclusive *trans*-selectivity (entries 2-7). Electronic effects exerted by phosphine ligands are similar to those found in the original oxygenative addition reaction, in which electron-donating or chelating ligands gave inferior results. While Tp–, Cp–, and Cp*–ligated ruthenium complexes exhibited compromised reactivity (entries 8-10), no β–lactam product was detected in the absence of a metal catalyst, supporting the intermediacy of a transition metal catalyst (entry 11).



2.1a (1.3 equiv) + **2.2a** (1.0 equiv) + **2.3a** (1.3 equiv) → **2.4a**

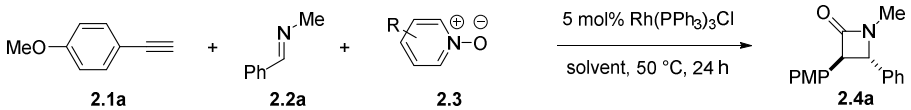
Entry	Catalyst	Yield (%)[a]	Entry	Catalyst	Yield (%)[a]
1	$[Rh(cod)Cl]_2/P(4\text{-}F\text{-}C_6H_4)_3$	90	7	$Rh(cod)_2BF_4/PPh_3$	90
2	$[Rh(cod)Cl]_2/P(C_6H_5)_3$	93	8	$TpRu(PPh_3)_2Cl$	0
3	$[Rh(cod)Cl]_2/P(4\text{-}MeO\text{-}C_6H_4)_3$	50	9	$CpRu(PPh_3)_2Cl$	8
4	$[Rh(cod)Cl]_2$/dppp	4	10	$Cp^*Ru(PPh_3)_2Cl$	38
5	$Rh(PPh_3)_3Cl$	93	11	none	0
6	$[Rh(cod)OH]_2/PPh_3$	32			

[a] Determined by ^1H NMR using hexamethylbenzene as an internal standard.

Table 2.1. Catalyst Screening for Oxygenative [2 + 2] Cycloaddition

Various oxidants and solvents were examined next. Among the oxidants tested with Wilkinson's catalyst, 4-picoline *N*-oxide (**2.1a**) gave the best result, giving β–lactam **2.4a** in 94% yield (Table 2.2, entry 1). Although pyridine *N*-oxide

(**2.3b**) showed comparable efficiency (entry 2), hygroscopic nature of **2.3b** caused hydrolysis of the starting imine. While both electron-rich and -deficient pyridine derivatives were shown to participate with lower efficiency (entries 3-5), a sulfoxide oxidant failed to induce transfer oxygenation (entry 6). Acetonitrile was outstanding among the solvents tested (entry 7), and other solvent systems – polar aprotic (entries 8-9) and nonpolar (entries 10-12) medium – furnished the product in low yield.



2.1a (1.3 equiv) + **2.2a** (1.0 equiv) + **2.3** (1.3 equiv) → **2.4a**

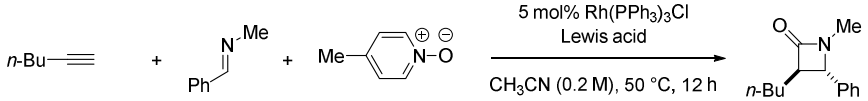
Entry	Oxidant[a]	Yield (%)[b]	Entry	Solvent[c]	Yield (%)[b]
1	4-picoline *N*-oxide (**2.3a**)	94	7	MeCN	93
2	pyridine *N*-oxide (**2.3b**)	73	8	DMF	22
3	4-methoxypyridine *N*-oxide (**2.3c**)	30	9	DMA	25
4	3,5-dichloropyridine *N*-oxide (**2.3d**)	14	10	DCE	25
5	8-methylquinoline *N*-oxide (**2.3f**)	10	11	THF	11
6	dimethyl sulfoxide (**2.5**)	0	12	toluene	14

[a] In CH_3CN (0.25 M).
[b] Determined by ^1H NMR using hexamethylbenzene as an internal standard.
[c] Using 4-picoline N-oxide (1.3 equiv) as oxidant in solvent (0.25 M).

Table 2.2. Oxidant and Solvent Screening

However, the optimized conditions were found to be ineffective for alkylalkyne **2.1b**, affording the corresponding lactam product **2.4b** in only 16% yield. With a hypothesis that a Lewis acid may facilitate the imine addition to

a ketene intermediate, a number of Lewis acid additives were examined (Table 2.3). Gratifyingly, addition of zinc chloride to the reaction mixture improved conversion significantly (entries 6-10). As the catalysis was deemed to depend largely on imine addition to a metallo-ketene intermediate, use of alkyne **2.1b** as limiting reagent gave a better result. Through screening experiments, a 1:1 ratio of rhodium and zinc species (entries 7 and 10) with slightly higher catalyst loadings has been determined to be optimal for alkylalkyne substrates.



2.1b (1.0 equiv) + **2.2a** (1.1 equiv) + **2.3a** (1.2 equiv) → **2.4b**

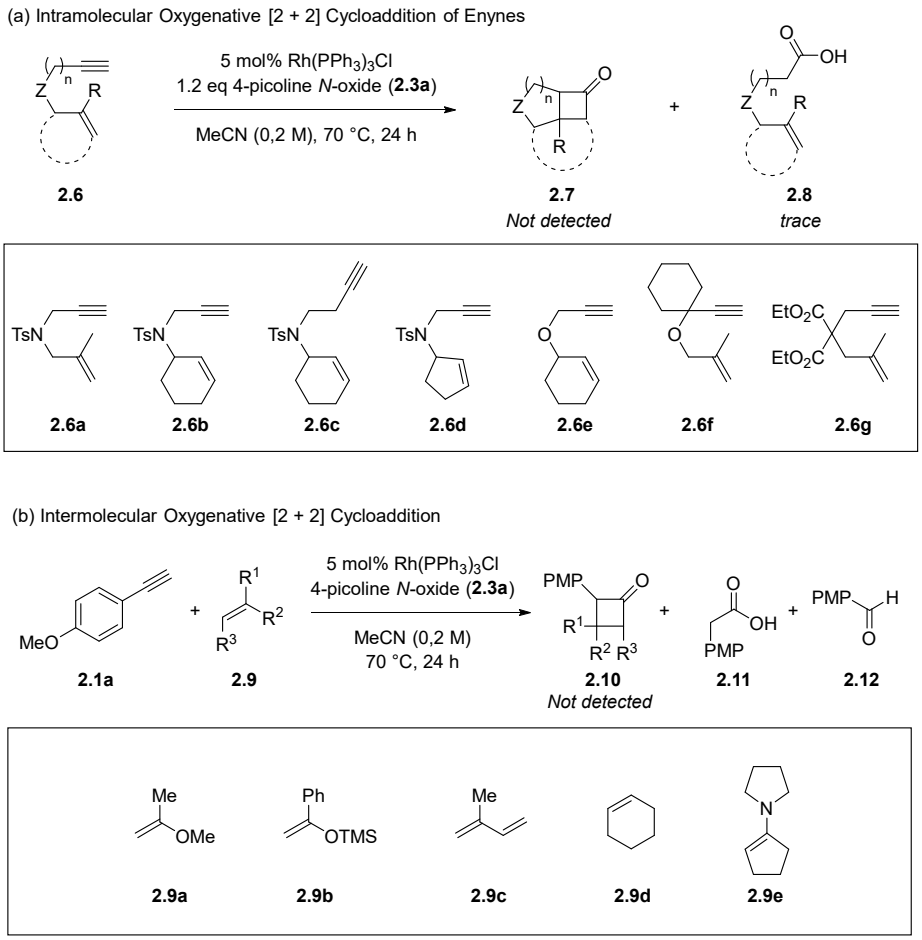
Entry	Lewis acid	Yield (%)[a]	Entry	Lewis acid	Yield (%)[a]
1	None	16	6	5 mol% $ZnCl_2$	63
2	10 mol% $TiCl_4$	0	7	10 mol% $ZnCl_2$	78
3	10 mol% $SnCl_4$	32	8	20 mol% $ZnCl_2$	53
4	10 mol% $ZnBr_2$	0	9	40 mol% $ZnCl_2$	44
5	10 mol% ZnI_2	38	10[b],[c]	15 mol% $ZnCl_2$	79

[a] Determined by ^1H NMR using hexamethylbenzene as an internal standard.
[b] 7.5 mol% $Rh(PPh_3)_3Cl$, 65 °C, 5 h.
[c] Isolated yield.

Table 2.3. Additive Screening for Alkylalkynes

Notwithstanding these promising outcomes from the reaction with imines, other [2 + 2] cycloaddition reactions known in the classic ketene-chemistry failed. Various enynes, designed for intramolecular [2 + 2] ketene–alkene

cycloaddition, were hardly oxygenated under the conditions, resulting in the formation of a complex mixture with no sign of the butanone product (Scheme 2.2a).



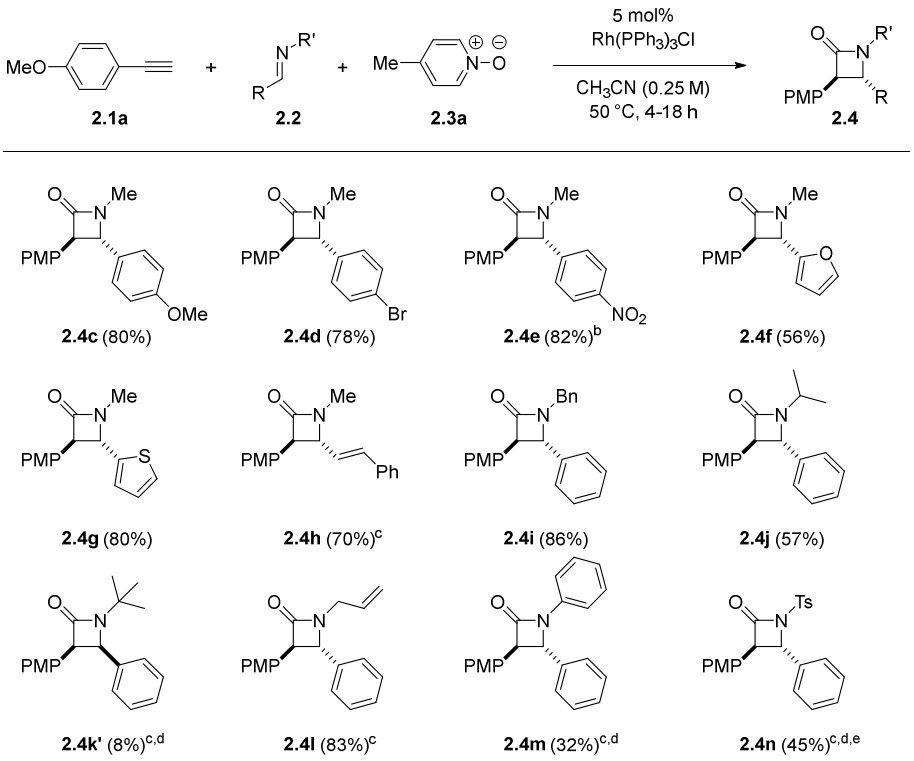
Scheme 2.2. Attempts toward [2 + 2] Cycloaddition with Alkenes

Based on the production of a small amount of carboxylic acid **2.8** indicating the viability of catalysis, intermolecular reaction was also screened, which

could avoid complications by chelation of the rhodium catalyst by enynes. However, several attempts using arylalkyne **2.1a** and alkenes **2.9** were unfruitful, with detection of carboxylic acid **2.11** and aldehyde **2.12**, which resulted from residual water addition and C–C bond cleavage,[6] respectively (Scheme 2.2b). In addition, the ketene [2 + 2] cycloaddition with aldehyde did not proceed either, which was confirmed by the experiments carried out by Dr. Dong Gil Lee.

2.1.3. Reaction Scope

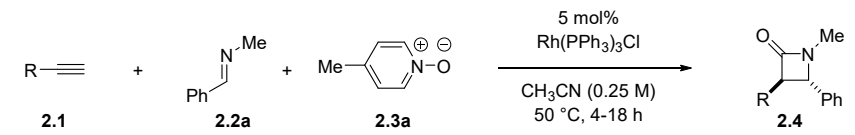
After establishing conditions for the β–lactam synthesis, the scope of the reaction was investigated starting from variations on the imine part. In the presence of Wilkinson's catalyst and 4-picoline *N*-oxide, the reaction of alkyne **2.1a** and an array of *N*-methyl imines afforded the corresponding β-lactam products in good yield (cf. **2.4c-2.4h**, Table 2.4). Electronic nature on the aryl group had little effects on reaction efficiency, while a minor quantity of *cis*-lactam was formed on use of *para*-nitrobenzylidene amine (cf. **2.4e**). Substituent effect on the nitrogen atom of the imine turned out to be crucial. While *N*-benzyl and *N*-allyl group proved to be excellent, a bulkier group and/or electronically-biased substituents, such as isopropyl, phenyl, tosyl, and *tert*-butyl groups, furnished β–lactams in much diminished yield. Several cases needed zinc chloride additive to assure acceptable conversion, presumably due to lower nucleophilicity of imines (e.g. **2.4h**, **2.4k'**, **2.4m**, and **2.4n)**.



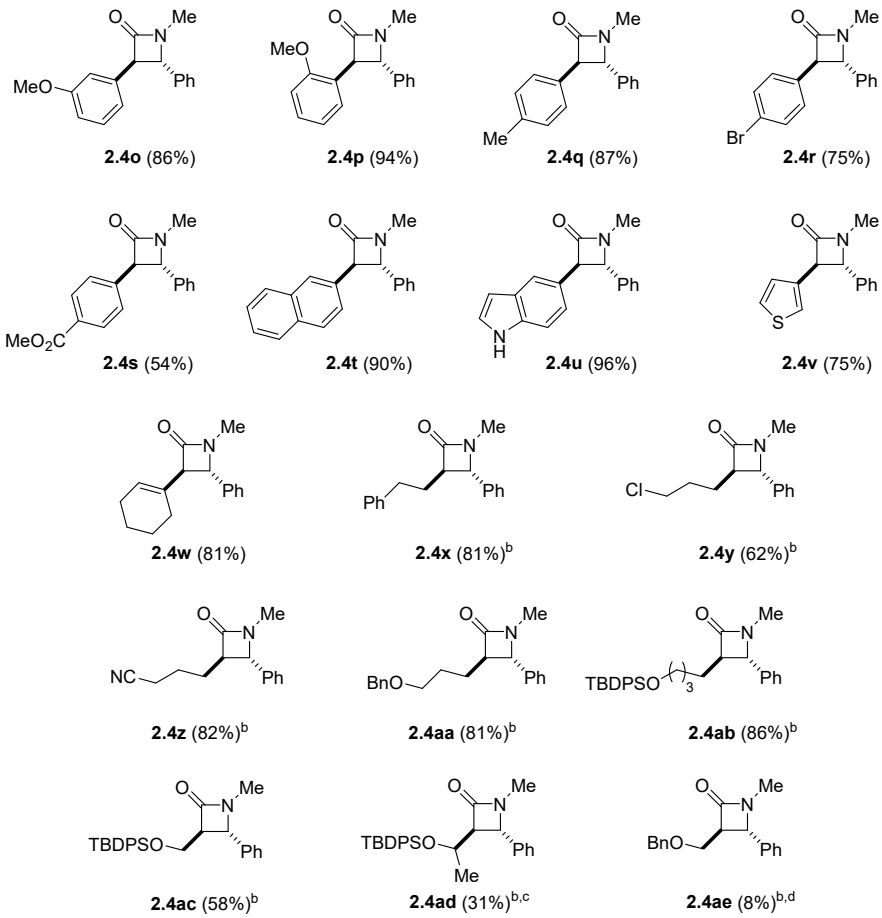
[a] General conditions: alkyne (0.65 mmol), imine (0.5 mmol), and 4-picoline *N*-oxide (0.65 mmol)
[b] *trans*:*cis* = 5.8:1
[c] Alkyne (0.5 mmol), imine (0.55 mmol), 4-picoline *N*-oxide (0.6 mmol), $Rh(PPh_3)_3Cl$ (0.0375 mmol, 7.5 mol%), and $ZnCl_2$ (0.075 mmol, 15 mol%) in CH_3CN (0.25 mL. 0.20 M) at 65 °C
[d] Imine recovered
[e] *trans*:*cis* = 7.7:1

Table 2.4. Oxygenative [2 + 2] Cycloaddition with Various Imines[a]

A variety of alkynes were capable of providing the β–lactams as well (Table 2.5). Arylalkynes participated in the reaction well, where arylalkynes bearing electron-donating and -withdrawing groups, as well as heteroarylalkynes all produced the desired lactams in good to excellent yields (cf. **2.4o**-**2.4v**).



2.1 **2.2a** **2.3a** **2.4**

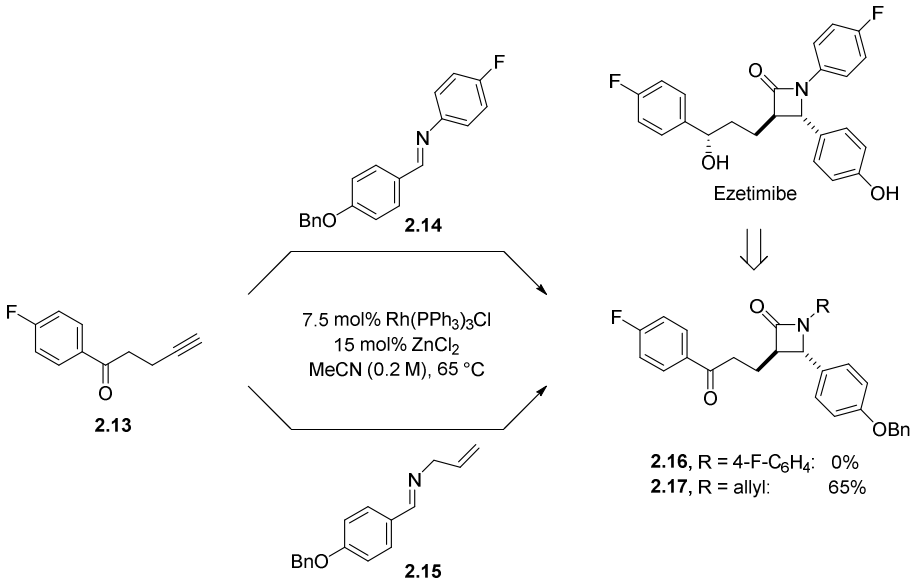


[a] General conditions: alkyne (0.65 mmol), imine (0.5 mmol), and 4-picoline *N*-oxide (0.65 mmol)
[b] Alkyne (0.5 mmol), imine (0.55 mmol), 4-picoline *N*-oxide (0.6 mmol), $Rh(PPh_3)_3Cl$ (0.0375 mmol, 7.5 mol%) and $ZnCl_2$ (0.075 mmol, 15 mol%) in CH_3CN (0.25 mL. 0.20 M) at 65 °C
[c] dr = 1:1; [d] 3-(Benzyloxy)-*N*-methylpropanamide was obtained in 46% yield.

Table 2.5. Oxygenative [2 + 2] Cycloaddition with Various Alkynes

While the reaction of a 1,3-enyne could be carried out using the conditions, alkylalkynes needed a zinc chloride additive as seen in Table 2.3. Alkyl

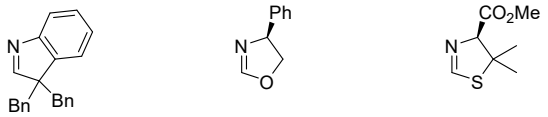
chloride and nitrile functionalities were tolerated under the conditions, as well as distal benzyl- and silyl ethers (**2.4y**-**2.4ab**). On the other hand, a proximal ether linkage had a large impact in that a propargyl silyl ether provided a poor yield of lactam **2.4ac**. More steric congestion at the propargylic position was also an inhibiting factor (cf. **2.4ad**), and benzyl propargyl ether furnished the lactam only in 8% yield, along with 47% of a *N*-methyl amide byproduct. These results imply the presence of chelating effects somewhere in the reaction pathways, which will be discussed in the following section.



Scheme 2.3. Synthetic Efforts toward Ezetimibe: An Unsuccessful Case

To further demonstrate the utility of the oxygenative [2 + 2] cycloaddition reaction, a concise synthesis of ezetimibe®, an approved cholesterol-lowering

drug,[7] was studied (Scheme 2.3). However, the reaction of alkyne **2.13** with *N*-arylimine **2.14** furnished no expected lactam, presumably due to the worst combination of the substrates: *e.g.* alkyl-substituted alkyne and electron-deficient aryl group on the imine nitrogen atom (cf. **2.4m**). Indeed, use of *N*-allyl imine **2.15** instead furnished lactam **2.17** in acceptable yield, supporting that an addition of the imine nitrogen to the metallo-ketene intermediate plays a critical role in overall catalysis. Unsuccessful imine counterparts also include sterically demanding imine **2.18** and electronically-biased imines **2.19** and **2.20** (Figure 2.1).

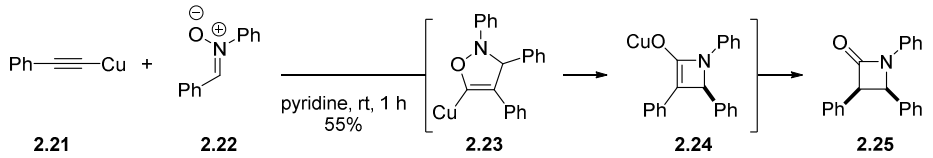


2.18 **2.19** **2.20**

Figure 2.1. Unsuccessful Substrates for the Oxygenative [2 + 2] Cycloaddition

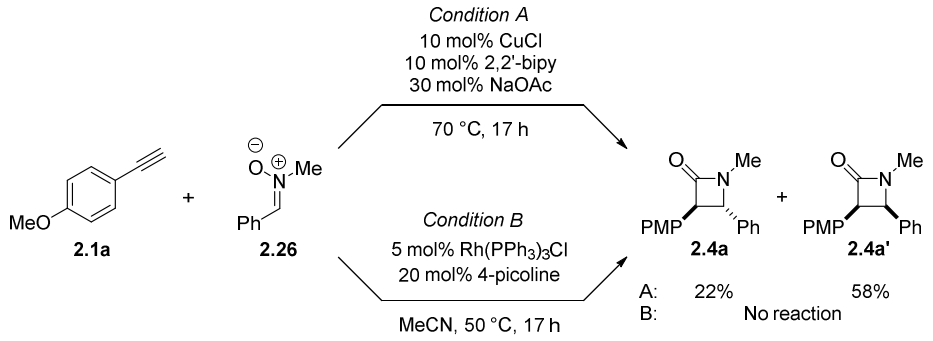
2.1.4. Mechanistic Studies

To gain insight into the mechanism, a series of experiments were carried out. Firstly, a possibility of intervention of the Kinugasa mechanism was examined, a known method for the synthesis of β–lactam from a terminal alkyne with a nitrone (Scheme 2.4).[8-11]



Scheme 2.4. The Kinugasa Reaction for the Synthesis of *cis*-β-Lactam

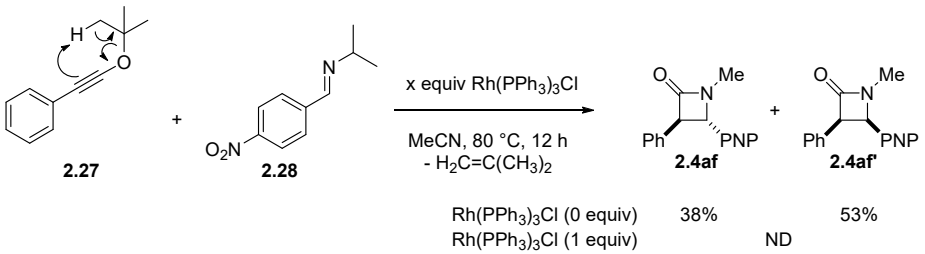
Alkyne **2.1a** and nitrone **2.26** did not react when $Rh(PPh_3)_3Cl$ was employed (Scheme 2.5, condition B), whereas the copper chloride catalyst was effective (condition A), supporting that the mechanism of the present oxygenative [2 + 2] cycloaddition is distinct from the Kinugasa reaction.[12] In addition, oxidation of imine by picoline *N*-oxide was not detected under our conditions, indicating that oxygen atom is transferred directly from picoline *N*-oxide to a vinylidenemetal, not through the nitrone.



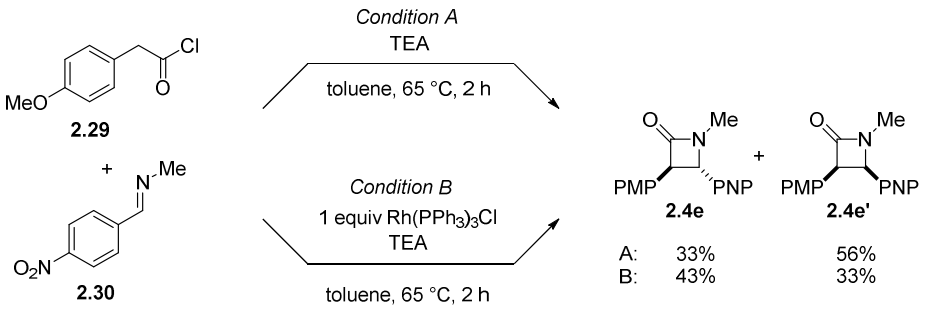
Scheme 2.5. A Control Experiment Excluding the Kinugasa Mechanism

Secondly, a nature of the ketene intermediate was investigated to shed light on the exceptional *trans*-selectivity. An initial experiment was designed to

generate a metal-free ketene from *tert*-butyl alkynyl ether **2.27**. A retro-ene-type ketene generation was feasible in the absence of Wilkinson's catalyst,[13] as seen in the formation of lactams **2.4af** and **2.4af'** in the presence of imine **2.28**. However, addition of a rhodium complex to the mixture inhibited this retro-ene process, leaving only starting materials **2.27** and **2.28** to be recovered (Scheme 2.6).



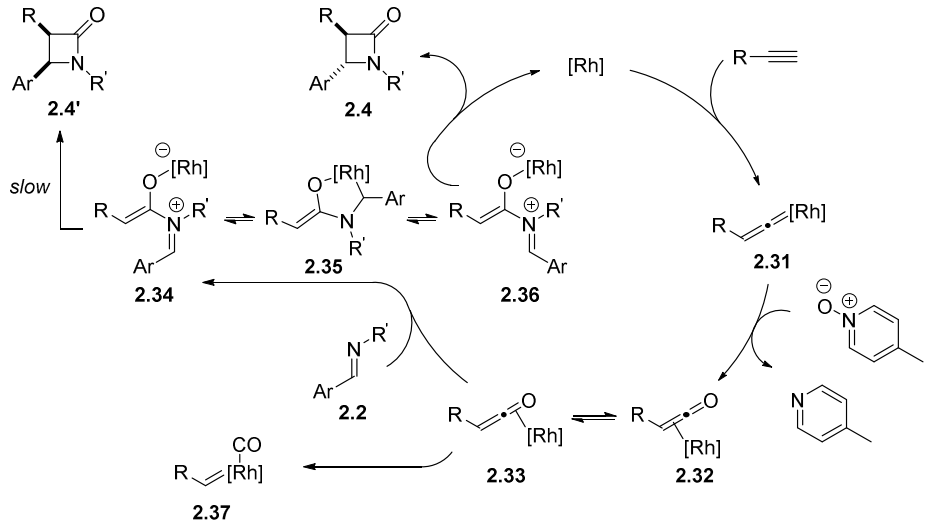
Scheme 2.6. A Rhodium-Bound Ketene: A Retro-Ene Approach



Scheme 2.7. A Rhodium-Bound Ketene: A Classic Approach

Gratifyingly, an alternative control experiment relying on a classical ketene-generation method gave a more discernible result. Under rhodium-free

conditions, the normal Staudinger reaction afforded the lactam products with *cis*-isomer **2.4e'** as the major product. However, in the presence of a stoichiometric Wilkinson's catalyst, the selectivity was reversed to favor *trans*-isomer **2.4e**, implying that the ketene was bound to the rhodium catalyst, switching stereoselectivity (Scheme 2.7).

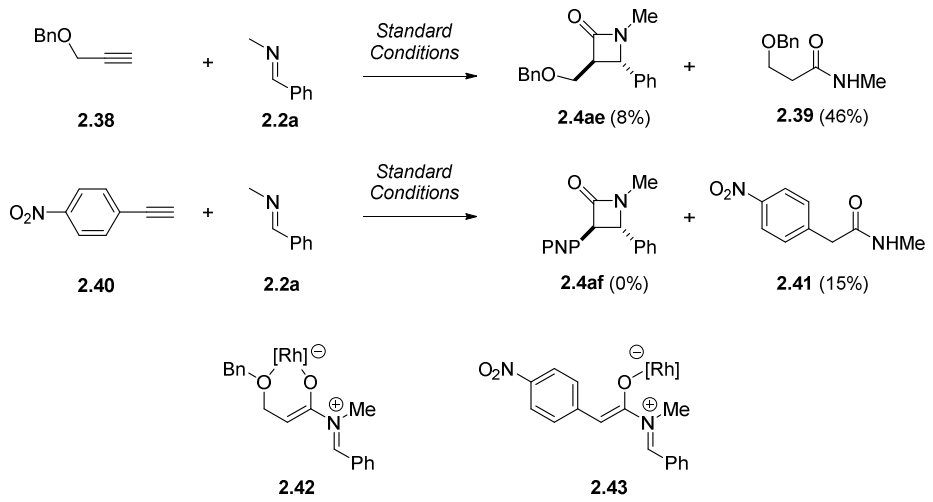


Scheme 2.8. Proposed Mechanism for the Oxygenative [2+2] Cycloaddition

On the basis of these experimental observations made during the reaction scope test, the mechanism of the oxygenative [2 + 2] cycloaddition is proposed as depicted in Scheme 2.8. Oxygenation of vinylidene rhodium **2.31** results in the formation of rhodium-bound ketene **2.32** and **2.33**. Upon addition of imine **2.2** to the metallo-ketene, zwitterionic complex **2.34** is initially formed. While the s-*cis*-iminium salt **2.34** can undergo electrocyclization process to give *cis*-

lactam **2.4'**, the rate of ring-closure seems to be slow due to the rhodium-coordination. Preceding to the electrocyclization appears to be the isomerization of the initial adduct to s-*trans*-iminium **2.36**, possibly through rhodacyclopentene intermediate **2.35**.[14] This more stable isomer **2.36** then undergoes conrotatory 4π–electrocyclization to afford *trans*-β-lactam **2.4**. Overall, the rhodium-bound intermediates are responsible for the stereoselective formation of the *trans*-β-lactam products by facilitating isomerization and/or retarding electrocyclization.

Mixing of stereoisomers in a number of cases could be rationalized on the basis of the proposed mechanism. For instance, an *N*-*tert*-butyl imine gave a *cis*-lactam (cf. **2.4k'**) exclusively, possibly through **2.34** that avoids allyl strain experienced in structure of **2.36** (R' = *tert*-butyl). Since the rate of electrocyclic ring-closure has been known to be increased with electrophilicity of iminum center,[15] *cis*-isomers were produced in minor quantities when 4-nitrobenzylideneamine and *N*-tosylimine were employed (cf. **2.4e** and **2.4n**). Zinc chloride is expected to activate the ketene intermediate, facilitating the imine-addition step relative to the deinsertion process of **2.33** that gives rhodium carbonyl complex **2.37**.



Scheme 2.9. Hydrolysis of Iminium Intermediate Leading to Amides

When the electrocyclization is slow, the iminium intermediates are hydrolyzed to amides (Scheme 2.9). For example, propargyl benzyl ether (**2.38**) preferentially afforded *N*-methyl amide **2.39**, in which a chelation effect may play a role in the retardation (cf. **2.42**). Nitrophenylalkyne **2.40** also yielded amide **2.43** only, where the electrocyclization was inhibited by diminished electron-density on the enolate part in this case (cf. **2.43**).

2.1.5. Conclusion and Outlook

Catalytic oxygenation of metal vinylidenes engendering metallo-ketene intermediates is applied to the expeditious synthesis of β–lactams. Various alkynes and imines can participate in the rhodium-catalyzed reaction, providing β–lactam products with high *trans*-selectivity. Mechanistic studies reveal that

the rhodium catalyst is tightly bound to the ketene intermediate, rendering this otherwise highly reactive and unstable intermediate viable in the reaction. Catalytic and controlled generation of a ketene intermediate is worth further exploration for the development of new reactions, and applications of our vinylidene-to-ketene transformation have been adopted by other groups as well.[16-18]

2.1.6. References

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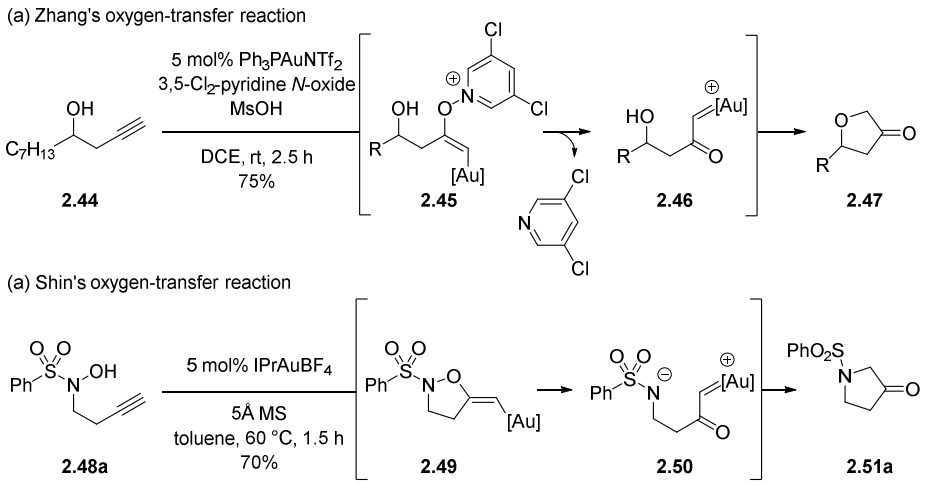
2.2. Ruthenium-Catalyzed Reconstitution Reaction of Terminal Alkynes with Intramolecular *N–O* and *N–N* Bonds

2.2.1. Introduction

Terminal alkynes become ketene surrogates, on use of an oxygen-transferring agent containing zwitterionic *N–O* bond. Meanwhile, other types of oxygenation reactions of alkynes have also been observed by utilizing oxidants with neutral *N–O* bonds as described in Chapter 1.

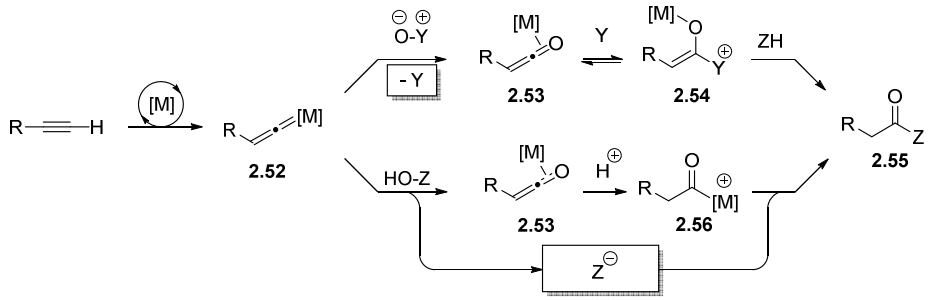


Scheme 2.10. Gold-Catalyzed Oxygenation Reactions of Alkynes

Interestingly, both types of oxygen-transferring agents can be employed in gold-catalysis. Zhang and coworkers demonstrated that using dichloropyridine *N*-oxide as an oxidant, an intermolecular oxygen-transfer reaction could occur to give rise to α–oxo gold carbenoid **2.46**, which was captured by a pendent hydroxyl group (Scheme 2.10a).[1] It should be pointed out that our vinylidene

oxygenation reaction and the Zhang's reaction are mutually complementary to each other in the regioselectivity perspective. On the other hand, Shin and coworkers reported an cycloisomerization reaction of alkynyl hydroxylamine **2.48a** to pyrrolidine-3-one **2.51a**, where the departing nitrogen atom recombined with the α–oxo gold carbenoid in **2.50** (Scheme 2.10b).[2]

An analogy can be made for vinylidenemetals (Scheme 2.11). Pyridine *N*-oxide derivatives liberate a pyridine moiety upon generation of a metallo-ketene intermediate, which may act as a nucleophilic catalyst for the subsequent acyl-substitution reaction (cf. **2.54**). On the other hand, hydroxylamine derivatives would produce anionic molecules, which subsequently conjoin with putative metallo-ketene or acylmetal complex (cf. **2.56**).

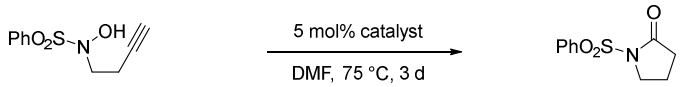


Scheme 2.11. Proposed Bond Cleavage and Recombination Reaction via Metal Vinylidene: A Reconstitution

We anticipated that a distinct mode of reactivity could be also found in the field of metal-vinylidene-mediated catalysis using neutral oxidizing agents, effecting "reconstitution" of a heteroatom–heteroatom bond at terminal alkynes.

2.2.2. Reaction Optimization for Hydroxylamines

Our efforts toward the development of an intramolecular reconstitution reaction commenced with rearrangement of homopropargylic hydroxylamine **2.48a**. Gratifyingly, **2.48a** smoothly rearranged to γ–lactam **2.57a** through a reaction using the commercial $CpRu(PPh_3)_2Cl$ catalyst. Screening experiments indicated that ruthenium(II) half-sandwich complexes were superior to rhodium(I) catalysts (entries 1-5 vs. entries 7-9, Table 2.6). A cyclopentadienyl ruthenium complex gave the best result among the catalysts tested, while a Cp*–Ru complex was also found to be competitive (entries 1-3). A phosphine ligand was highly beneficial as the phosphine-free system, such as $CpRu(MeCN)_3PF_6$, gave the product in much diminished yield over a prolonged reaction period (entry 4). While DMF was shown to be an optimal solvent, a range of media, such as DCE, MeCN, THF, and toluene, all afforded the lactam product more than 80% yield.



2.48a **2.57a**

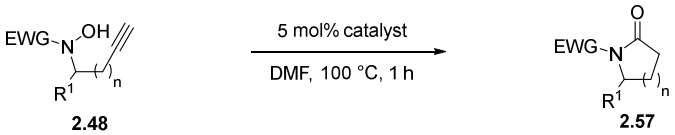
Entry	Catalyst	Yield (%)[b]	Entry	Catalyst	Yield (%)[b]
1	$CpRu(PPh_3)_2Cl$[c]	90	6	$[RuCl_2(p\text{-cymene})]_2$	38
2	$CpRu(PPh_3)_2Cl$[d]	92	7	$Rh(PPh_3)_3Cl$	0
3	$Cp^*Ru(PPh_3)_2Cl$	78[e]	8	$RhCl_3$	0
4	$CpRu(CH_3CN)_3PF_6$	18[e]	9[f]	$[RhCl(cod)]_2$ + $P(4\text{-}F\text{-}C_6H_4)_3$	0
5	$TpRu(PPh_3)_2Cl$	20[e]			

[a] Alkyne **2.48a** (0.1 mmol), catalyst (0.005 mmol) in DMF (0.5 mL) at 75 °C
[b] Determined by ^1H NMR using 1,3,5-tri-*tert*-butylbenzene as an internal standard.
[c] 5 h; [d] 100 °C, 1 h; [e] starting material remained; [f] 3 mol% catalyst and 12 mol% ligand

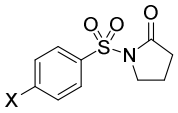
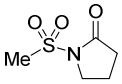
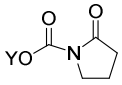
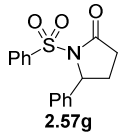
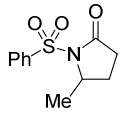
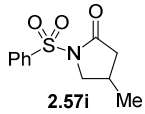
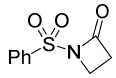
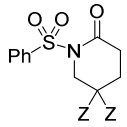
Table 2.6. Catalyst Screening for Reconstitution Reaction[a]

2.2.3. Reaction Scope for Hydroxylamines

Having the optimized conditions in hand, variations at the hydroxylamine structure were examined. A range of sulfonyl groups were all tolerated to furnish *N*-sulfonyl lactams in good yields (entries 1-4, Table 2.7), whereas carbamate analogs resulted in compromised yields of the reconstitution product (entries 5-6). While a Thorpe-Ingold effect was observed for homologated systems (entries 12-13), adding a substituent on the tether adjacent to nitrogen was detrimental to reaction efficiency for 5-membered lactam formations (entries 7-8). While production of 3-oxopyrrolidine (cf. **2.51h**, Scheme 2.12) was responsible for diminished yield in MeCN solvent, this gold-catalysis-like

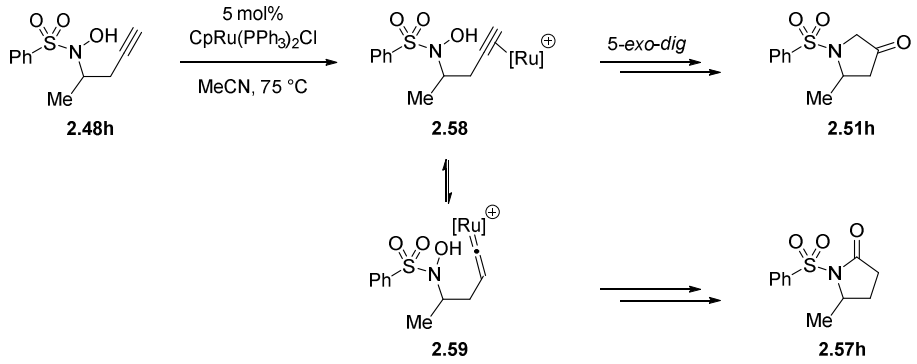


2.48 **2.57**

Entry	Product		Yield (%)[b]
1 2 3	 **2.57a-2.57c**	**a:** X = H **b:** X = Me **c:** X = NO_2	90 86 94
4	 **2.57d**		84
5[c] 6[c]	 **2.57e, 2.57f**	**e:** Y = Bn **f:** Y = *t*-Bu	36 41
7	 **2.57g**		47
8 9[d]	 **2.57h**		48 98
10[c]	 **2.57i**		97
11	 **2.57j**		72
12 13	 **2.57k, 2.57l**	**k:** Z = H **l:** Z = Me	10 71

[a] An alkyne (1.0 mmol), $CpRu(PPh_3)_2Cl$ (0.05 mmol) in DMF (10 mL) at 100 °C
[b] Isolated yield; [c] 60 °C, 1 d; [d] 60 °C, 40 h

Table 2.7. Reaction Scope for Reconstitution Reaction of Hydroxylamines



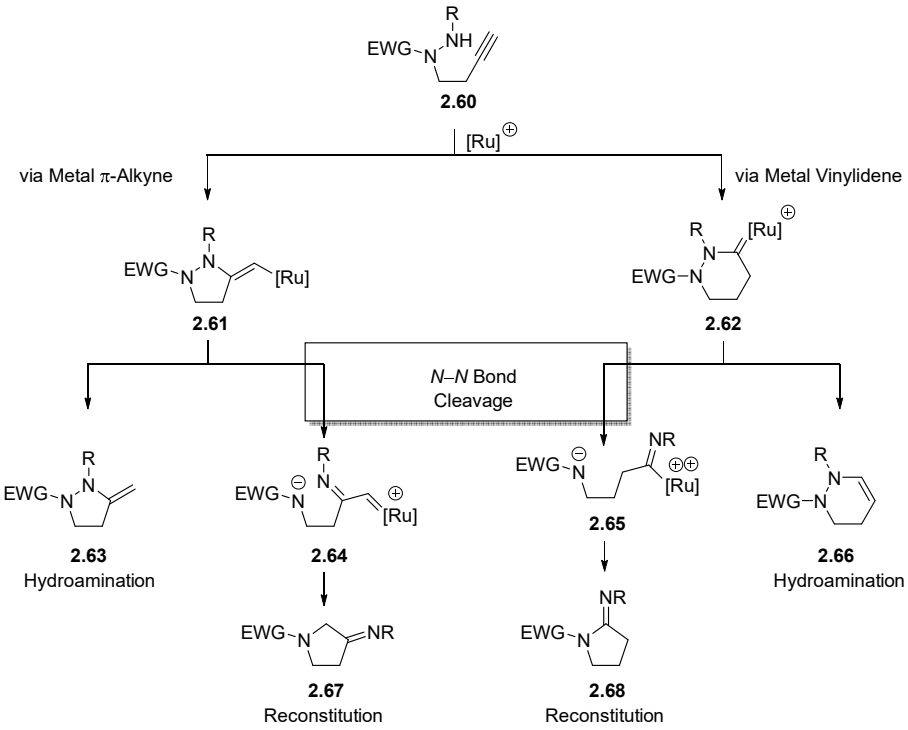
Scheme 2.12. Competition between π-Acid- and Vinylidene Mechanisms

product (see Scheme 2.10a) was not detected in DMF solvent. Rather than mechanistic divergence, the lifetime of the catalyst seems to be problematic. Indeed, a prolonged reaction time at a lower temperature furnished a nearly quantitative amount of lactam product **2.57h** (entry 9). A propargylic hydroxylamine also worked affording β–lactam **2.57j** in good yield (entry 11).

2.2.4. Reaction Screening for Hydrazines

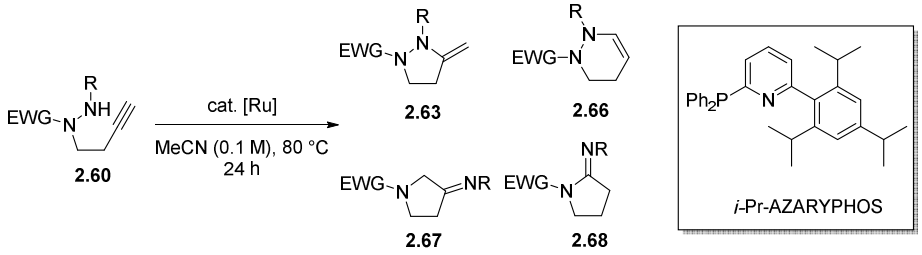
Having established optimistic results in the reconstitution reaction of hydroxylamines, we turned our attention to analogous reconstitution using hydrazines derivatives. Under the similar mechanistic postulation, hydrazines were expected to give cyclic amidine products. However, π–alkyne activation mode (cf. **2.58**, Scheme 2.12) appeared to become more pronounced in this case, due to the increased nucleophilicity of the transferred atom, nitrogen. Therefore, more detailed postulations were needed that could account for four possible

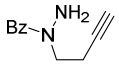
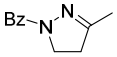
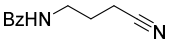
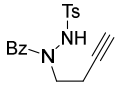
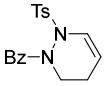
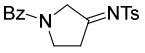
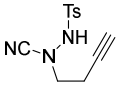
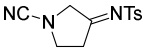
products, by categorizing π–acid versus vinylidene mechanisms, and whether the bond-cleavage event took place or not (Scheme 2.13).



Scheme 2.13. Possible Pathways of Alkynylhydrazine Reconstitution

Indeed, every possible scenario in the postulations has been observed to be played out. For example, benzoylhydrazine **2.60a** gave π-acid/hydroamination (PH) product **2.63a** from the catalysis of a Cp–Ru complex, along with a small amount of vinylidene/reconstitution (VR) product in the form of nitrile **2.69** (entry 1, Table 2.8). Distribution of the product was changed on the use of more vinylidene-friendly ligand AZARYPHOS,[3-5] giving **2.69** in 35% yield along



Entry	Substrate	Catalyst	Product	
1	 **2.60a**	**A**: 10 mol% $CpRu(PPh_3)_2Cl$	 **2.63a** (84%)	 **2.69** (4%)
2		**B**: 10 mol% $CpRu(naphthalene)PF_6$ 20 mol% *i*-Pr-AZARYPHOS	**2.63a** (60%)	**2.69** (35%)
3	 **2.60b**	**B**	 **2.66b** (71%)	 **2.67b** (16%)
4[a],[b],[c]	 **2.60c**	**B**	 **2.68c** (24%)	 **2.67c** (27%)

[a] Reaction was conducted with 20 mol% of ruthenium precatalyst and 40 mol% of *i*-Pr-AZARYPHOS ligand in MeCN (0.05 M) at 70 °C for 12 h.
[b] Yields were determined by ^1H NMR.
[b] Starting materials were remained in 36% yield.

Table 2.8. Ruthenium-Catalyzed Isomerization Reactions of Alkynylhydrazines

with **2.63a** in 60% yield (entry 2). In contrast, 1-tosyl-2-benzoylhydrazine **2.60b** produced vinylidene/hydroamination (VH) product **2.66b** with π–

acid/reconstitution (PR) product **2.67b** (entry 3). While formation of nitrile compound **2.69** (entry 1) indicates that the vinylidene mechanism was intervened, more supportive example can be found from cyanamide **2.60c**, where cyclic amidine **2.68c** was obtained in 45% yield along with inseparable PR product **2.67b** (entry 4). Overall, all possible four isomerization modes of alkynylhydrazines have been realized.

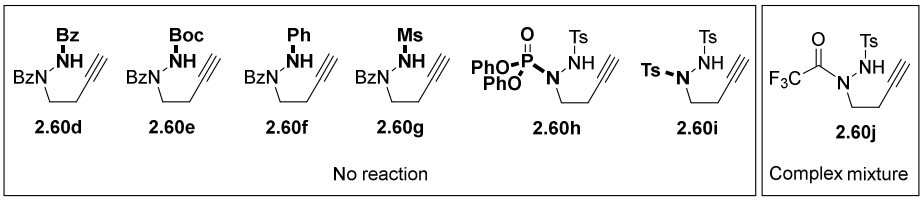
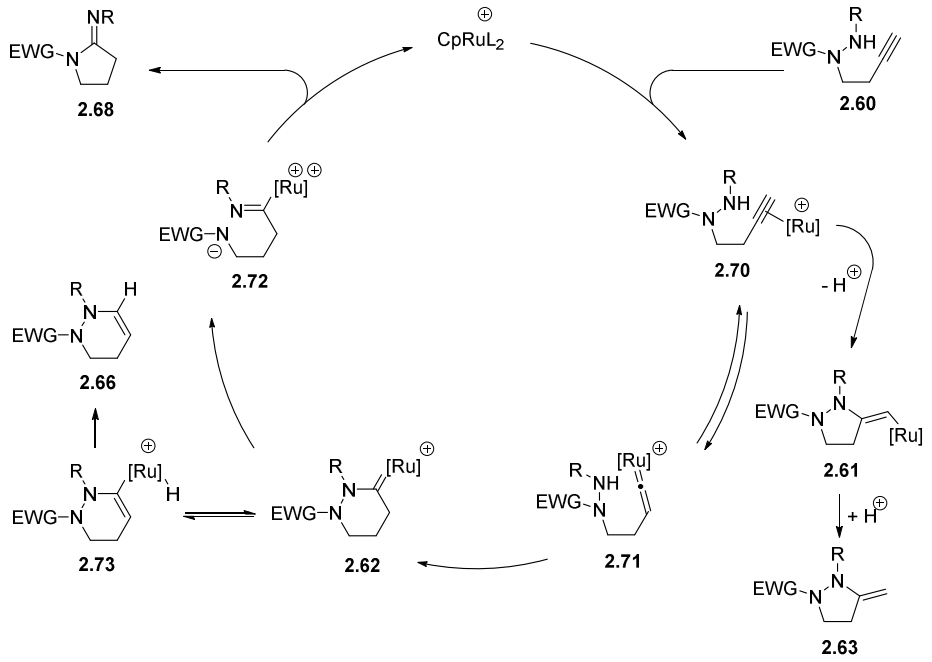


Figure 2.2. Unsuccessful Substrates for the Reconstitution of Alkynyl Hydrazine

In addition, it was found that hydrazide **2.60d**, carbazate **2.60e**, phenylhydrazine **2.60f**, and methanesulfonylhydrazide **2.60g** were not nucleophilic enough under the standard conditions, exhibiting no reactivity. Not only the substituent on the nucleophilic nitrogen, but also that of the departing nitrogen was found to be important as 2-phosphonohydrazine **2.60h** and 1,2-bistosylhydrazine **2.60i** gave no detectable isomerization products in contrast to other 1-tosylhydrazides that resulted in cycloisomerization (cf. **2.60b** and **2.60c**). Increased activation by adding a trifluoromethyl group on 2-position led to formation of a complex mixture under the conditions.

2.2.5. Proposed Mechanism

The mechanism for the intramolecular reconstitution reaction of alkynylhydrazines is proposed in Scheme 2.14. Initial π-alkyne complex **2.70** can undergo a direct addition reaction to furnish **2.61**, which is responsible for the formation of a diazine (PH) and a 3-oxopyrrolidine (PR). In the meanwhile, the vinylidene center of ruthenium complex **2.71**, existing in equilibrium with **2.70**, can be attacked by the pendent nitrogen atom generating aza–Fisher carbene **2.62**. While isomeric alkenylruthenium **2.73** leads to another hydroamination product (VH), a competitive bond-cleavage process is also viable giving iminylruthenium(IV) complex **2.72** that gives rise to amidine **2.68** (VR). The reconstitution reaction of hydroxylamines in Sections 2.2.2 and 2.2.3 may follow the same mechanism, while vinylidene/reconstitution (VR) pathway is dominant in this case.



Scheme 2.14. Proposed Mechanism for the Intramolecular Reconstitution

2.2.6. Conclusion and Outlook

With dynamic equilibria involving ruthenium vinylidene- and ruthenium π–alkyne complexes, we have shown that every competitive mode of the reaction is possible. At the same time, metal vinylidene-mediate catalysis is revealed to hardly override other modes of reaction pathways in intramolecular settings.

Empirical results imply that the vinylidene pathway may be favored with a more acidic proton on the transferring moiety, in accordance with literature examples of intermolecular nucleophilic addition to vinylidenemetals.[6-10] Since hydroxylamine derivatives have highly acidic proton,[11] development of intermolecular oxygenating hydroxylamine reagents can be viable.

Intermolecular oxygen-transfer may be advantageous in terms of regioselectivity, because the entropic factor no longer assists the π–acid mechanism over the vinylidene mechanism. Thus, we set out to develop the intermolecular reconstitution reaction using hydroxylamine derivatives.

2.2.7. References

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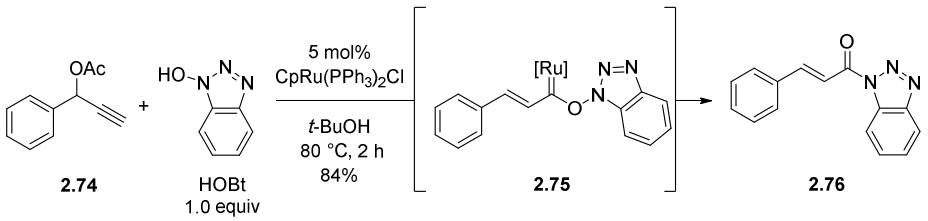
2732.

2.3. Ruthenium-Catalyzed Amidation Reaction of Terminal Alkynes

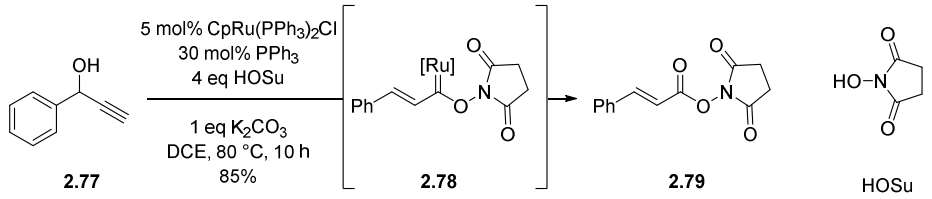
2.3.1. Reaction Optimization

Addition of hydroxylamines to a ruthenium vinylidene complex was investigated in an intermolecular setting. Gratifyingly, the reaction of propargylic acetate **2.74** with one equivalent of *N*-hydroxybenzotriazole (HOBt) furnished reconstitution product **2.76** (Scheme 2.15). Propargylic acetate **2.74** is assumed to undergo a vinylidene- or allenylidene ruthenium-mediated addition process to produce Fischer carbene **2.75**. This Fischer carbene is believed to be responsible for the formation of **2.76** through *N–O* bond cleavage/recombination.



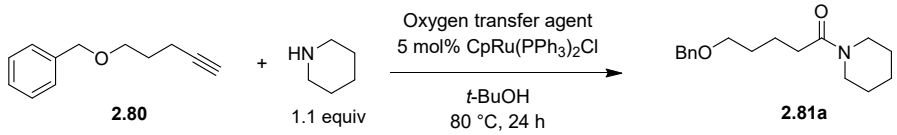
Scheme 2.15. Intermolecular Reconstitution Reaction with HOBt

It is worthy of note that the use of *N*-hydroxysuccinimide (HOSu) instead of HOBt exhibits different reaction stoichiometry. Propargyl alcohol **2.77** furnished *N*-hydroxylsuccinimide ester **2.79** under the same catalyst system, and excess amount of HOSu was necessary (Scheme 2.16). On the basis of the literature precedent (cf. Scheme 1.6), the mechanism is expected to be direct oxidation of Fischer carbene **2.78** by an external HOSU molecule in this case.



Scheme 2.16. Formation of *N*-Hydroxysucciniminyl (NHS) Ester from a Terminal Alkyne

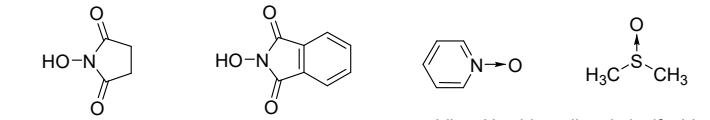
N–Acyl benzotriazole is a well-known carboxylic acid derivative for its aptitude toward acyl substitution, which has been widely investigated by Katritzky and coworkers.[1] Gratifyingly, the reconstitution reaction of aliphatic terminal alkyne **2.80** underwent excellently in the co-presence of amine nucleophiles, and the in situ acyl-substitution gave rise to amide product **2.81a** (Table 2.9). An array of oxidants was screened next. While *N*–hydroxyimides, dimethyl sulfoxide, and pyridine *N*–oxide were found to be inapplicable (entries 1-4), *N*–hydroxybenzotriazole and its aza-derivatives were excellent mediator for the amidation (entries 6 and 7). *N*–Tosylhydroxylamine was ineffective (entry 5), implying the mechanism of the present reaction to be different from intramolecular reconstitution of Section 2.2. Further studies were focused on structural variation of hydroxytriazole systems. The presence of two nitrogen atoms on the azole ring was crucial (entries 10-11 vs entry 12), and a



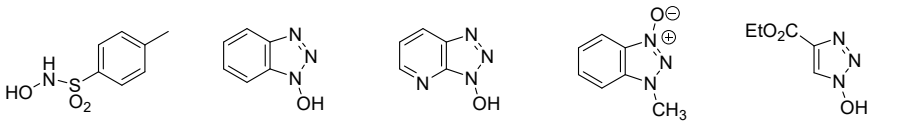
2.80 **2.81a**

Entry	Oxygen transfer agent	Yield (%)[b]
1	*N*-hydroxysuccinimide (HOSU)	17
2	*N*-hydroxyphthalimide	15
3	pyridine *N*-oxide	1
4	dimethyl sulfoxide	0
5	*N*-hydroxytoluenesulfonamide	1
6	1-hydroxybenzotriazole (HOBt)	93[c]
7	1-hydroxy-7-aza-benzotriazole (7-HOAt)	89[c]
8	1-methylbenzotriazole-3-oxide	0
9	ethyl-1-hydroxytriazole-4-carboxylate	97[c]
10	indazol-1-ol	45
11	benzoimidazol-1-ol	97[d]
12[e]	indol-1-ol	0
13	no oxygen source	0

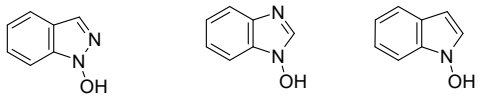
[a] Reaction conditions: alkyne (0.1 mmol), oxygen source (0.2 mmol), piperidine (0.11 mmol), $CpRu(PPh_3)_2Cl$ (0.005 mmol), and *t*-BuOH (0.25 mL) at 80 °C for 24 h
[b] Determined by GC with 1,3,5-trimethoxybenzene as an internal standard
[c] Reaction for 1 h [d] Reaction for 16 h
[e] *O*-TBS protected indol-1-ol was deprotected using TBAF and used directly without further purifications, due to instability of indol-1-ol.



N-hydroxysuccinimide *N*-hydroxyphthalimide pyridine *N*-oxide dimethylsulfoxide

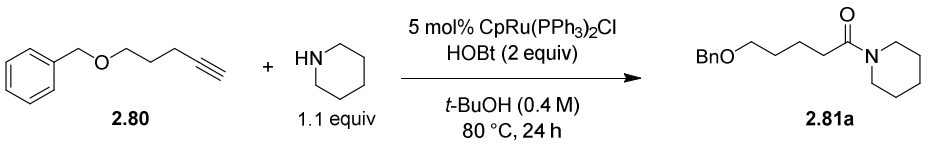


N-hydroxytoluene-sulfonamide 1-hydroxybenzotriazole 1-hydroxy-7-aza-benzotriazole 1-methylbenzo-triazole-3-oxide ethyl-1-hydroxytriazole-4-carboxylate



indazol-1-ol benzoimidazol-1-ol indol-1-ol

Table 2.9. Oxidant Screening for the Amidation Reaction[a]



2.80 1.1 equiv **2.81a**

Entry	Deviations from standard conditions	Yield (%)[b]
1[c]	None	90
2	5 mol% $IndRu(PPh_3)_2Cl$ instead of $CpRu(PPh_3)_2Cl$	54
3	5 mol% $Cp^*Ru(PPh_3)_2Cl$	85
4	5 mol% $TpRu(PPh_3)_2Cl$	9
5	5 mol% CpRu(dppm)Cl	34
6	5 mol% $Ru(PPh_3)_3Cl_2$	6
7	5 mol% $Rh(PPh_3)_3Cl$	4
8	no catalyst	0
9	DCE instead of *t*-BuOH	95
10	Toluene instead of *t*-BuOH	94
11	THF instead of *t*-BuOH	89
12	H_2O instead of *t*-BuOH	73[d]
13	40 °C instead of 80 °C	89
14	1 equiv BtOH	90
15	0.5 mol% $CpRu(PPh_3)_2Cl$	84

[a] Reaction conditions: alkyne (0.1 mmol), HOBt (0.2 mmol), piperidine (0.11 mmol), $CpRu(PPh_3)_2Cl$ (0.005 mmol), and *t*-BuOH (0.25 mL) at 80 °C for 24 h
[b] Determined by GC with 1,3,5-trimethoxybenzene as an internal standard
[c] Reaction for 1 h [d] Corresponding carboxylic acid was formed as a byproduct

Table 2.10. Screening of Other Parameters for the Amidation Reaction[a]

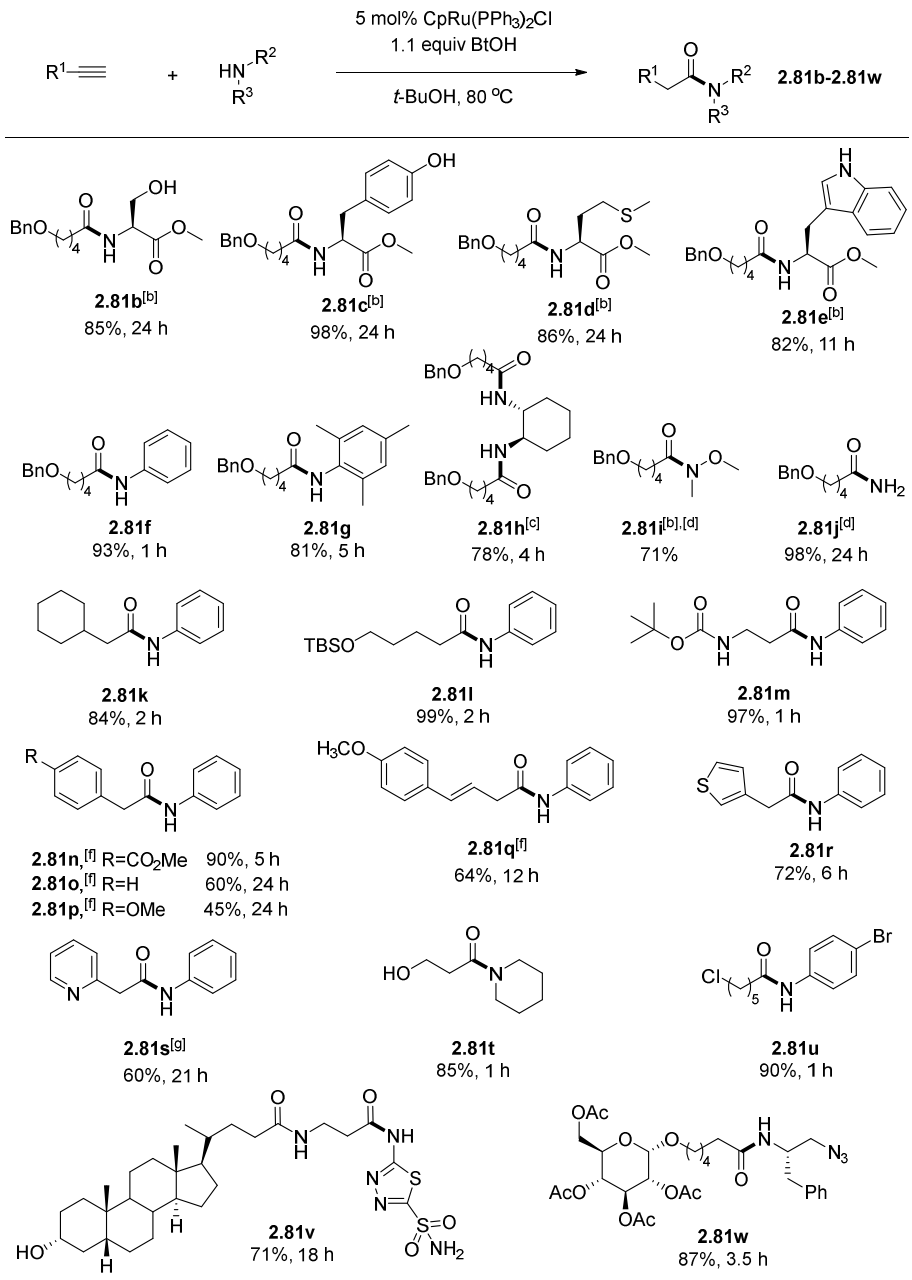
non-benzofused triazole also exhibited comparable efficiency (entry 9). However, zwitterionic triazole-oxide was inactive for the amidation reaction (entry 8).

Further optimization studies revealed that half-sandwich ruthenium complexes are decent catalysts (Table 2.10. entries 1-5 vs entry 6), while a ruthenium complex with a chelating ligand exhibited lower efficiency (entry 5). Most of solvent systems are adaptable for the amidation reaction giving generally over 90% yields (entries 10-12). The reaction undergoes slowly at 40

°C, yet requiring only one hour at 80 °C (entries 13 and 1). A reduced amount of HOBt was not detrimental to the yield nor to reaction times, and a lower loading of the catalyst caused only minuscule loss of chemical yield.

2.3.2. Reaction Scope

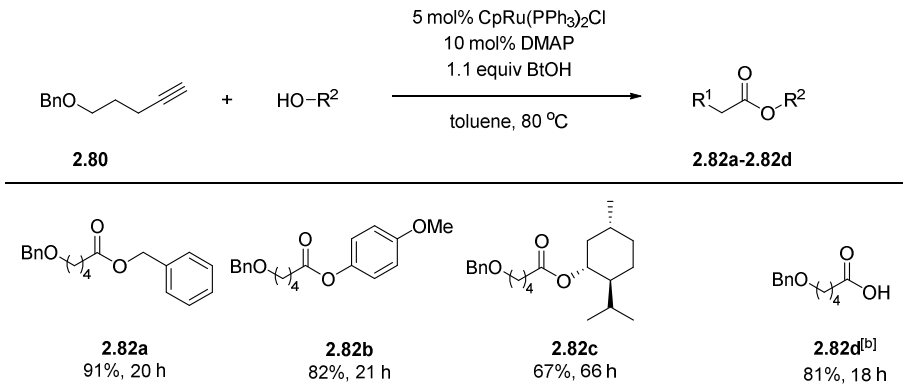
The ruthenium-catalyzed amidation reaction, making use of terminal alkynes as an acyl donor, has been tested for a variety of amine nucleophiles (Table 2.11). Amino acid derivatives, such as serine-, tyrosine-, methionine-, and tryptophan methyl esters, are competent nucleophiles even without protection on free hydroxyl functionalities (cf. **2.81c**). *N*-Aryl amides, primary amide, and Weinreb amide can be prepared using this reaction. Of note, *N*,*O*-dimethylhydroxylamine was dehydrogenated under reaction conditions giving formaldehyde *O*-methyloxime. Thus Weinreb amide **2.81j** was synthesized in a stepwise manner. Various alkyl-, alkenyl-, and arylalkynes all proved to be competent, furnishing corresponding anilide products in good yields (cf. **2.81k**–**2.81s**). Even within a more complex molecular setting, carbonic anhydrase inhibitor[2] **2.81v** could be synthesized from a lithocholic acid derivative. An azide-containing amine nucleophile is also capable of undergoing the amidation reaction, without intervention of the click reaction (cf. **2.81w**).[3,4]



[a] Reaction conditions: alkyne (0.5 mmol), HOBt (0.55 mmol), amine (0.55 mmol), $CpRu(PPh_3)_2Cl$ (0.025 mmol), and *t*-BuOH (1.25 ml) at 80 °C
[b] amine•HCl (0.55 mmol), $NaHCO_3$ (1.0 mmol) [c] amine (0.275 mmol)
[d] Ruthenium catalysis without amine for 1 h, then addition of amine at rt. 19 h [e] $NH_4CO_2NH_2$ (0.75 mmol)
[f] $CpRu(PPh_3)_2Cl$ (0.05 mmol), HOBt (2.0 mmol) [g] toluene (0.4 M)

Table 2.11. Substrate Scope: Amine Nucleophiles[a]

A number of oxygen-centered nucleophiles were examined briefly. In these cases, DMAP is required to catalyze acyl-substitution reaction from the initial acyl-benzotriazole intermediate. Benzyl-, aromatic-, and aliphatic alcohols are shown to be applicable giving esters in good yields, as well as water nucleophile for the synthesis of a carboxylic acid (Table 2.12).



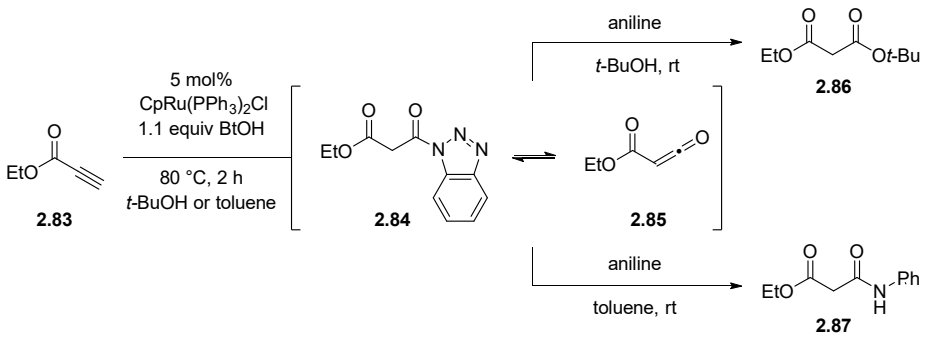
2.82a	**2.82b**	**2.82c**	**2.82d**[b]
91%, 20 h	82%, 21 h	67%, 66 h	81%, 18 h

[a] Reaction conditions: alkyne (0.5 mmol), HOBt (0.55 mmol), alcohol (0.55 mmol), $CpRu(PPh_3)_2Cl$ (0.025 mmol), DMAP (0.05 mmol), and toluene (1.25 mL) at 80 °C
[b] Reaction conditions: alkyne (0.5 mmol), HOBt (0.55 mmol), $CpRu(PPh_3)_2Cl$ (0.025 mmol), and t-butanol (1.25 mL) and sat.$NaHCO_3$ (aq) (0.25 mL) at 80 °C

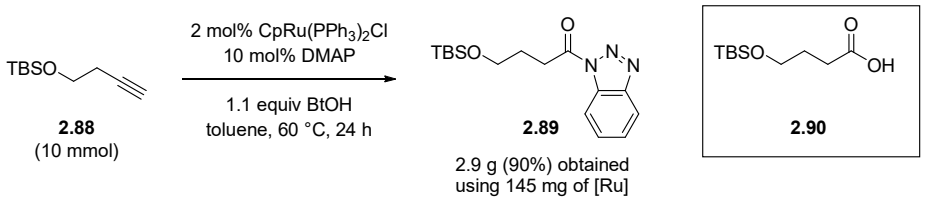
Table 2.12. Substrate Scope: Alcohol Nucleophiles[a]

There are a few cases where the modification of the procedure is needed. When propiolate **2.83** was subjected to the standard conditions, *tert*-butyl ethyl malonate (**2.86**) was obtained instead of malonamide **2.87**, presumably via ketene intermediate **2.85** (Scheme 2.17). Moreover, facile 1,4-addition of aniline to the starting propiolate was also problematic. Thus, addition of aniline nucleophile needed to be carried out after ruthenium-catalysis, using toluene as the solvent. Similar adjustment of the procedure was applied for the preparation

of 2-pyridylacetamide **2.81s** in Table 2.11, where ketene-avoiding conditions was needed due to the presence of acidic benzylic proton (vide supra).



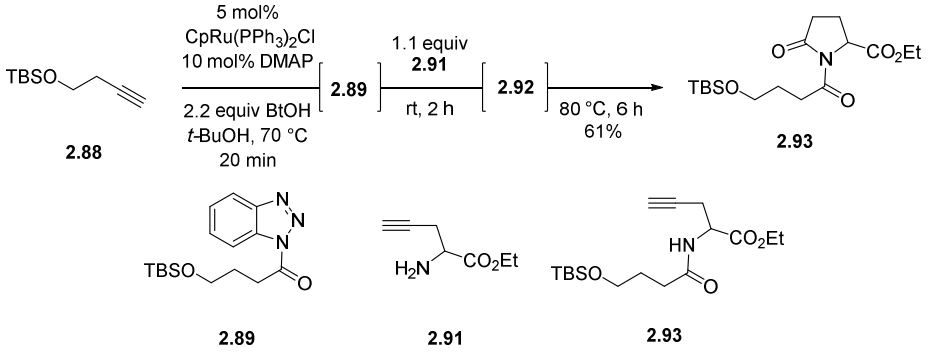
Scheme 2.17. Putative Intervention of Ketene Intermediate from a Propiolate



Scheme 2.18. Gram-Scale Synthesis of an Acyl-Benzotriazole Having Acid-Sensitive Tail

One advantageous feature of the amidation reaction is that acid-sensitive groups are well tolerated. For example, a γ-*tert*-butyldimethylsilyloxy moiety is not compatible with a carboxylic acid, thus making compound such as **2.90** an unattainable intermediate for the synthesis of γ-hydroxycarboxylic acid derivatives. However, the corresponding acyl-benzotriazole **2.89**, an acyl

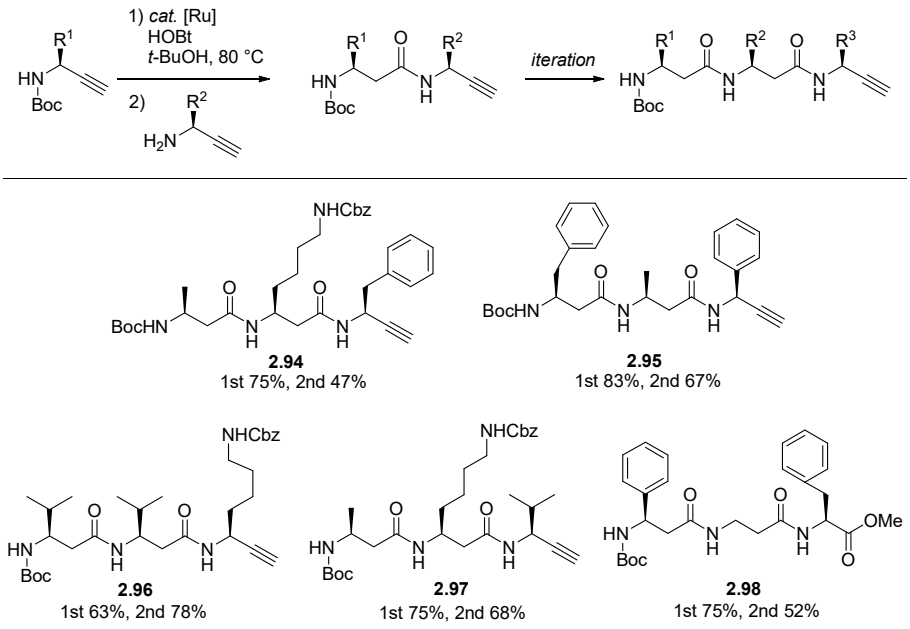
surrogate, was prepared in gram-scale using only 2 mol% of the ruthenium catalyst (Scheme 2.18).



Scheme 2.19. Temperature-Separated Iterative Amidation

Unlike the ketene chemistry presented in Section 2.1, the acyl-benzotriazole intermediate is stable enough to be accumulated in the reaction mixture. In addition, the ruthenium-catalyzed acyl-benzotriazole formation is shut down at ambient temperature, whereas the nucleophilic acyl-substitution process occurs at this range of temperatures. A demonstration taking advantage of the separation of two reaction modalities, reconstitutive addition and substitution, is shown in Scheme 2.19. After alkyne **2.88** was converted to acyl-benzotriazole **2.89** by the ruthenium catalysis, propargyl amine **2.91** was added at ambient temperature for acyl-substitution. Upon completion of the first amide formation, increasing of temperature restarted the catalysis producing imide **2.93** in good yield. Overall, two catalytic reactions and two acyl substitution reactions are carried out in a planned order by temperature control.

The ruthenium-catalyzed amidation is therefore applicable for the synthesis of polyamides such as β–peptides. Without any protection on the alkyne part, a number of tripeptides are prepared in this manner (Table 2.13). Since the poor solubility of peptides was the major factor that compromised the reaction yields, this solution-phase result promises the possible improvement in solid-phase β–peptide synthesis. As the chemical- and biological space of β–peptides are expanding rapidly, our present methods can serve as a useful tool for the preparation of the bio-mimicking polyamide.[5.6]

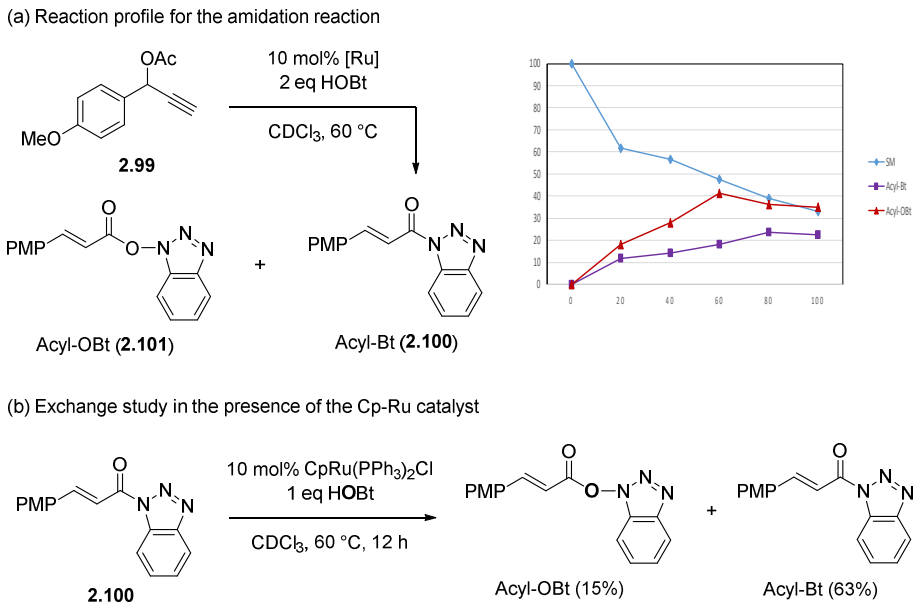


Reaction conditions: 1) alkyne (1 equiv), HOBT (1.1 equiv), $CpRu(PPh_3)_2Cl$ (5 mol%), DMAP (10 mol%), toluene or *t*-butanol (0.2 M), 80 °C, 2-12 h; 2) amine or aminoalkyne (1 equiv), *t*-butanol (0.2 M), rt or 80 °C, 1-24 h

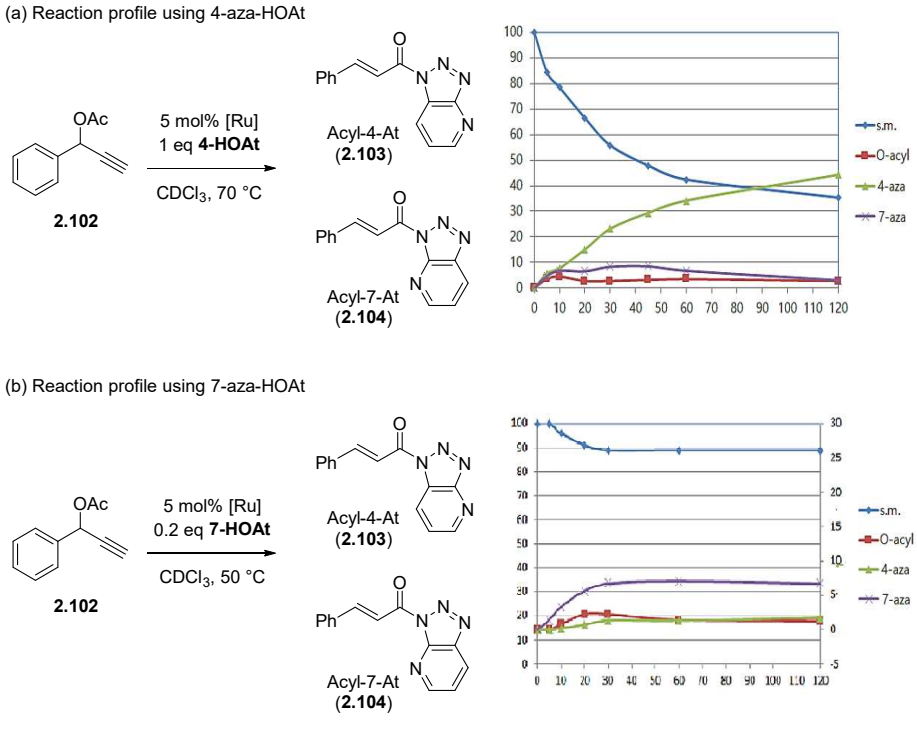
Table 2.13. Iterative Amidation Reaction for β-Peptide Synthesis

2.3.3. Mechanistic Studies

The mechanism of oxygenative NHS ester formation (Scheme 2.16) probably involves oxidation of Fisher carbene by *N*-hydroxysuccinimide, as the reaction conditions are very similar to the oxidative alkynol cyclization developed by Rhee and Trost (see Scheme 1.6 and 1.7). The amidation using benzotriazole derivatives may follow the same. The reaction profile shows that substantial amount of *O*-acyl hydroxybenzotriazole (**2.101**, Acyl–OBt) was formed at the initial phase of the reaction of propargylic acetate **2.99**, (Scheme 2.20a). However, it was revealed that benzotriazole group of **2.100** was exchangeable with HOBt in the presence of the Cp–Ru catalyst, rendering the reaction profile hard to interpret.



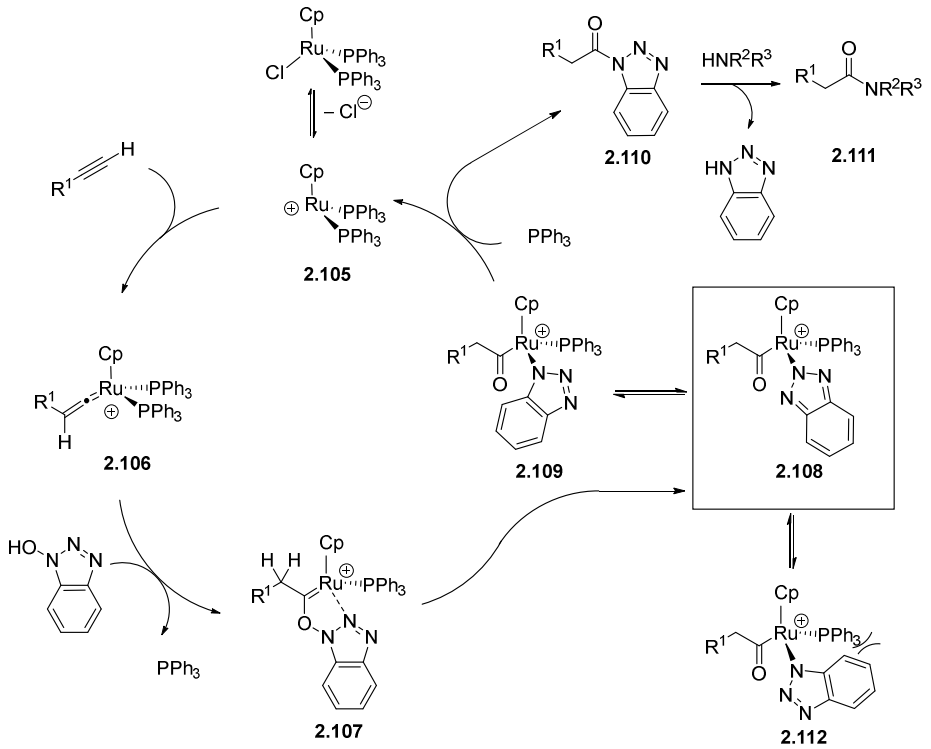
Scheme 2.20. Reaction Profile and Exchange Between Acyl-OBt and Acyl-Bt



Scheme 2.21. Reaction Profiles Using 4-Aza- and 7-Azahydroxybenzotriazoles

Reaction profiles using 4-aza and 7-azahydroxybenzotriazoles (HOAt) suggest another mechanistic scenario. Each isomer of HOAt gave rise to a stereospecific product at the initial phase: 4-HOAt and 7-HOAt furnished acyl-4-At **2.103** and acyl-7-At **2.104** as the major products, respectively (Scheme 2.21a and 2.21b).[7] Since innate nucleophilicity is largely inclined toward the

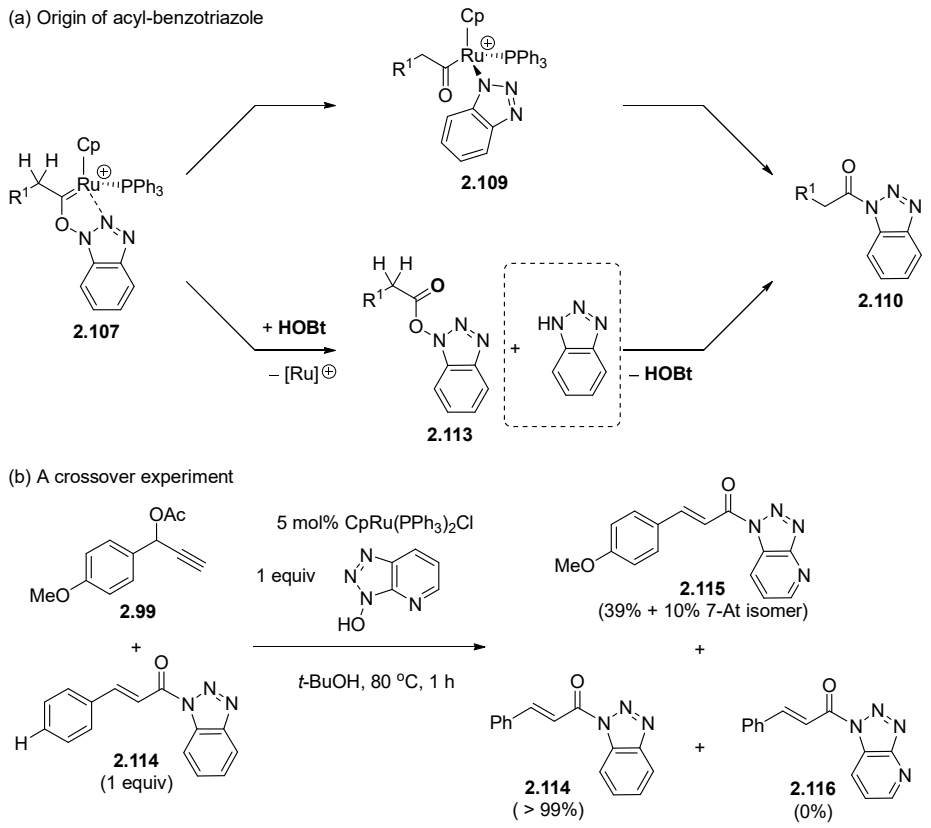
formation of acyl-4-At (Scheme 2.21c), a sequence involving the Fischer carbene oxidation by an external hydroxyazole and the acyl-substitution of an acyl-OAt intermediate is highly unlikely, which would exhibit such a preference of acyl-4-At formation.



Scheme 2.22. Proposed Mechanism: An Internal Redox-Isomerization

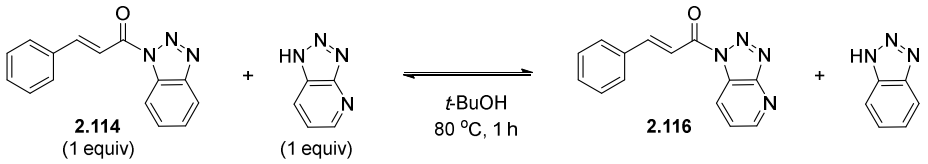
Our new mechanistic proposal is delineated in Scheme 2.22. Upon formation of ruthenium vinylidene **2.106** and subsequent addition of hydroxybenzotriazole, Fischer carbene complex **2.107** is generated. The coordination of 2-nitrogen atom of the azole ring to the ruthenium center leads

to internal redox-isomerization, affording transiently-dearomatized acylruthenium 2-azolyl complex **2.108**. An isomerization to **2.109** and reductive elimination give rise to acyl-benzotriazole **2.110**, from which the acyl-substitution occurs to give carboxamide **2.111** in the presence of an amine nucleophile. Conservation of stereochemical information observed in Scheme 2.21 can be explained by this scenario, in which isomerization to **2.112** is disfavored due to the steric clash exerted by the triphenylphosphine ligand.



Scheme 2.23. Crossover Experiment in the Presence of Acyl-Bt

The proposed internal-redox mechanism would not liberate a free benzotriazole, in contrast to the Fischer carbene oxidation mechanism (Scheme 2.23a). An azole-scavenging experiment was designed to distinguish the two mechanisms. In the presence of one equivalent of cinnamyl-Bt **2.114**, the reaction of **2.99** with 7-AtOH, a less nucleophilic *N*–hydroxyazole, furnished methoxy-substituted acyl-At **2.115** without any sign of cinnamyl-At **2.116**. Since the free aza-benzotriazole could substitute cinnamyl-Bt **2.114** (Scheme 2.24), the result of the crossover experiment suggested that the free-azole was not generated during the reaction, indicating the proposed mechanism to be more viable than the Fisher-carbene oxidation mechanism.



Scheme 2.24. Scrambling between Acyl-Bt and Aza-benzotriazole

2.3.4. Conclusion

A ruthenium-catalyzed protocol for amidation of terminal alkynes has been developed. Multiple chemical bonds are reconstituted through the catalysis mediated by the ruthenium vinylidene, providing an isolable intermediate acyl-benzotriazole. In the presence of amine nucleophiles, subsequent acyl substitution is immediately followed, producing carboxamide derivatives in

excellent yields. This amidation reaction can be carried out with a broad range of alkyne and amine substrates, using an operationally simple procedure. In addition, the separation of reconstitution and acyl substitution processes makes it possible to perform iterative polyamide synthesis, providing new opportunities for the further application.

Described in Chapter 2 of this dissertation are three distinct types of oxidative functionalization of terminal alkynes mediated by transition metal vinylidenes. The rhodium-catalyzed oxygenation employs external zwitterionic oxygenating agents to generate a metallo-ketene intermediate, from which a new C–C bond is emanating at the β–carbon through [2 + 2] cycloaddition (Chapter 2.1). The ruthenium-catalyzed reconstitutive cycloisomerization demonstrates that a hydroxylamine is a suitable oxygen-transfer agent toward metal vinylidene complexes, as well as a hydrazine for the nitrogen-transfer process (Chapter 2.2). Described in the last part of Chapter 2 is evolution of hydroxyazole compounds as the external oxygenating agent that enables clean and controllable amidation of terminal alkynes.

The potential of metal-vinylidene-mediated-catalysis, especially that of mediating redox-active transformations, will continue to be explored. With the principal mode of oxygenative and nitrogenative functionalizations of terminal alkynes presented here, we anticipate broad applications to be followed taking advantage of the new acyl-equivalent, not only in the field of organic synthesis, but in the chemical space of biochemistry and material sciences.

2.3.5. References

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2.4. Experimental Sections

2.4.1. General Information

All commercially available reagents were purchased at highest commercial quality and used as received. Anhydrous solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour. Yields refer to spectroscopically pure compounds unless otherwise stated. The progress of reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 ml of concentrated sulfuric acid in 250 ml of ethanol), a ninhydrin solution (200 mg of ninhydrin and 5 mg 10% acetic acid in 95 ml butanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 mL of 5% NaOH solution in 300 mL of water), or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60). All solvents were used after passing through activated alumina columns of solvent purification systems from Glass Contour. Commercially available reagents were purchased from Sigma-Aldrich, Strem, TCI, Acros, or Alfa Aesar. NMR spectra were obtained on a Bruker DPX-300 (300 MHz), an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million (δ) relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz (Hz). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High performance liquid chromatography data and mass spectra were obtained on a Shimadzu LCMS-2020 (LC-20AD pump, SPD-20A UFLC version UV-VIS detector, LCMS-2020 mass spectrometer, CTA-20A column oven, FRC-10A fraction collector), Thermoscientific Syncronis C18 column

(ID 4.6 mm, 5 μm particle size, 150 mm length) system. Unless otherwise stated, HPLC system was operated under binary solvent system (A = acetonitrile/TFA 99.9:0.1, B = H_2O/TFA 99.9:0.1), flow rate 1.0 ml/min, column temperature 40 ºC. Gas chromatography data were obtained on a Hewlett Packard HP 6890 Series GC system. High resolution mass spectra were obtained from Organic Chemistry Research Center at Sogang University.

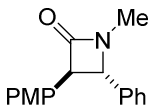
2.4.2. Experimental Procedures and Characterization Data

2.4.2.1. Oxygenative [2+2] Cycloaddition Reaction

General Procedure A: Oxygenative [2+2] Cycloaddition of Arylalkynes
To an oven-dried vial equipped with a screw-cap were added an alkyne (0.65 mmol, 1.3 equiv), an imine (0.50 mmol, 1 equiv), 4-picolin *N*-oxide (70.9 mg, 0.65 mmol, 1.3 equiv), $Rh(PPh_3)_3Cl$ (23.1 mg, 0.025 mmol, 5 mol%), and CH_3CN (2.0 mL, 0.25 M). After flushing with argon gas, the vial was capped and sealed. The resulting yellow solution was heated at 50 ºC, and monitored by TLC analysis. Upon complete consumption of the starting imine, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. Purification by flash chromatography on a silica gel column afforded β-lactam product in an analytically pure form.

General Procedure B: Oxygenative [2 + 2] Cycloaddition of Alkylalkynes
To an oven-dried vial equipped with a screw-cap were added an alkyne (0.50 mmol, 1 equiv), an imine (0.55 mmol, 1.1 equiv), 4-picolin *N*-oxide (65.5 mg, 0.60 mmol, 1.2 equiv), $Rh(PPh_3)_3Cl$ (34.7 mg, 0.0375 mmol, 7.5 mol%), $ZnCl_2$ (0.5 M in THF, 0.15 mL, 0.075 mmol, 15 mol%), and CH_3CN (2.5 mL, 0.20 M). After flushing with argon gas, the vial was capped and sealed. The resulting yellow solution was heated at 50 ºC, and monitored by TLC analysis. Upon complete consumption of the starting alkyne, the reaction mixture was cooled

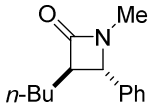
to ambient temperature and concentrated *in vacuo*. Purification by flash chromatography on a silica gel column afforded β-lactam product in an analytically pure form.



***trans*-3-(4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (2.4a)**[1]

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.3a** (125 mg, 93%) as a yellow oil. R_f 0.16 (hexane-EtOAc, 3:1).

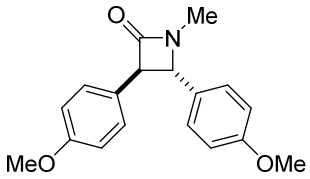
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.40 (s, 1H), 4.10 (s, 1H), 3.78 (s, 3H), 2.85 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 159.2, 137.6, 129.3, 128.7, 128.6, 127.3, 126.3, 114.4, 65.8, 65.3, 55.4, 27.1.



***trans*-3-butyl-1-methyl-4-phenylazetidin-2-one (2.4b)**

Following the general procedure B, the reaction of alkyne **2.1b** (41.1 mg, 0.50 mmol) with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4b** (85.8 mg, 79%) as a yellow oil. R_f 0.30 (hexane-EtOAc, 3:1).

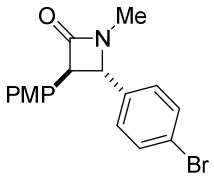
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 4.13 (s, 1H), 2.93 (t, *J* = 7.8 Hz, 1H), 2.73 (s, 3H), 1.91 – 1.80 (m, 1H), 1.77 – 1.65 (m, 1H), 1.44 – 1.21 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 138.3, 129.2, 128.4, 126.3, 63.1, 61.5, 29.6, 28.6, 27.0, 22.7, 14.0.; IR (neat): ν_{max} 2956, 2629, 1747, 1456, 1388, 699 cm^{-1}.; HRMS (FAB) calcd. for $C_{14}H_{19}NO$ (M+H): 218.1546, found 218.1545.



***trans*-3,4-bis(4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (2.4c)**

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2c** (74.6 mg, 0.50 mmol) [2] gave **2.4c** (119.2 mg, 80%) as a yellow oil. R_f 0.09 (hexane-EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 4H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.34 (d, *J* = 1.6 Hz, 1H), 4.08 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.83 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 160.1, 159.3, 129.5, 128.7, 127.8, 127.5, 114.7, 114.5, 65.6, 65.4, 55.6, 55.5, 27.1.; IR (neat): ν_{max} 2936, 1747, 1512, 1246, 1175, 1031, 835 cm^{-1}.; HRMS (FAB) calcd. for $C_{18}H_{19}NO_3$ (M+H): 298.1444, found 298.1443.

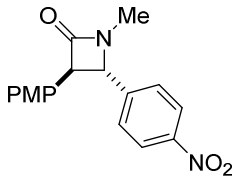


***trans*-4-(4-bromophenyl)-3-(4-methoxyphenyl)-1-methylazetidin-2-one (2.4d)**

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2d** (99.0 mg, 0.50 mmol)[2] gave **2.4d** (135.3 mg, 78%) as a yellow oil. R_f 0.16 (hexane-EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 2H), 7.24 – 7.15 (m, 4H), 6.93 – 6.84 (m, 2H), 4.35 (d, *J* = 2.2 Hz, 1H), 4.07 (s, 1H), 3.80 (s, 3H), 2.85 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 159.4, 136.8, 132.6, 128.7, 128.1, 127.0, 122.8, 114.6, 65.6, 65.4, 55.5, 27.3.; IR (neat): ν_{max} 2936, 1753, 1514, 1250, 826 cm^{-1}.; HRMS (FAB) calcd. for $C_{17}H_{16}BrNO_2$ (M+H): 346.0443, found

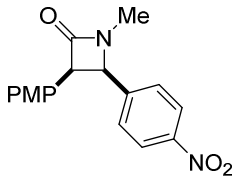
346.0443.



***trans*-3-(4-methoxyphenyl)-1-methyl-4-(4-nitrophenyl)azetidin-2-one (2.4e**)

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2e** (82.1 mg, 0.50 mmol)[2] gave **2.4e** (109.2 mg, 70%) as a yellow oil. R_f 0.09 (hexane-EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.26 (m, 2H), 7.56 – 7.46 (m, 2H), 7.23 – 7.15 (m, 2H), 6.95 – 6.86 (m, 2H), 4.51 (d, *J* = 2.2 Hz, 1H), 4.10 (s, 1H), 3.81 (s, 3H), 2.91 (d, *J* = 0.7 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.6, 148.3, 145.3, 128.7, 127.2, 126.4, 124.7, 114.7, 66.0, 65.2, 55.6, 27.6.; IR (neat): ν_{max} 2937, 1753, 1514, 1249, 1179, 735 cm^{-1}.; HRMS (FAB) calcd. for $C_{17}H_{16}N_2O_4$ (M+H): 313.1189, found 313.1188.

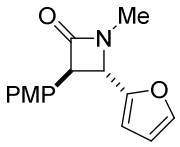


***cis*-3-(4-methoxyphenyl)-1-methyl-4-(4-nitrophenyl)azetidin-2-one (2.4e'**)

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2e** (82.1 mg, 0.50 mmol)[2] gave **2.4e** (18.1 mg, 12%) as a yellow oil. R_f 0.29 (hexane-EtOAc, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 5.02 (d, *J* = 5.6 Hz, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 3.66 (s, 3H), 2.95 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 158.8, 147.5, 143.3, 129.8, 128.1, 123.9, 123.6, 113.9, 61.9, 61.5, 55.2, 27.8.; IR (neat): ν_{max} 2917, 1755, 1515, 1346, 855, 732 cm^{-1}.; HRMS (FAB)

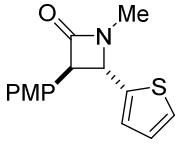
calcd. for $C_{17}H_{16}N_2O_4$ (M+H): 313.1189, found 313.1183.



***trans*-4-(furan-2-yl)-3-(4-methoxyphenyl)-1-methylazetidin-2-one (2.4f)**

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2f** (54.6 mg, 0.50 mmol)[3] gave **2.4f** (72.3 mg, 56%) as a yellow oil. R_f 0.09 (hexane-EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.0 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.92 – 6.86 (m, 2H), 6.42 – 6.39 (m, 2H), 4.44 (s, 2H), 3.80 (s, 4H), 2.83 (s, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 159.3, 150.5, 143.6, 128.7, 127.0, 114.5, 110.8, 109.5, 61.6, 58.6, 55.5, 27.3.; IR (neat): ν_{max} 2940, 2836, 1751, 1514, 1248, 1179, 1032, 796, 741 cm^{-1}.; HRMS (FAB) calcd. for $C_{15}H_{15}NO_3$ (M+H): 258.1131, found 258.1130.

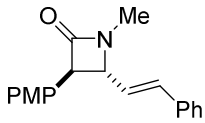


***trans*-3-(4-methoxyphenyl)-1-methyl-4-(thiopene-2-yl)-azetidin-2-one (2.4g)**

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2g** (62.6 mg, 0.50 mmol)[4] gave **2.4g** (109.6 mg, 80%) as a yellow oil. R_f 0.16 (hexane-EtOAc, 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.08 – 7.02 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 4.66 (d, *J* = 2.1 Hz, 1H), 4.26 (s, 1H), 3.80 (s, 3H), 2.87 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.4, 141.5, 128.7, 127.6, 127.0, 126.2, 126.0, 114.5, 66.0, 61.6, 55.5, 27.2.; IR (neat): ν_{max} 2998, 2835, 1749, 1611, 1513, 1386, 1247, 1031, 705 cm^{-1}.; HRMS (FAB)

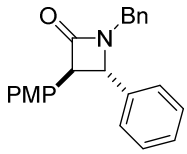
calcd. for $C_{15}H_{15}NO_2S$ (M+H): 274.0902, found 274.0902.



***trans*-3-(4-methoxyphenyl)-1-methyl-4-((E)-styryl))azetidin-2-one (2.4h)**

Following the general procedure B, the reaction of alkyne **2.1a** (66.1 mg, 0.50 mmol) with imine **2.2h** (79.9 mg, 0.55 mmol)[5] gave **2.4h** (103.9 mg, 70%) as a yellow oil. R_f 0.09 (hexane-EtOAc, 3:1).

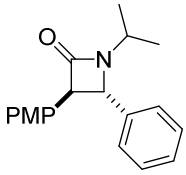
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.25 (m, 3H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 15.8, 8.7 Hz, 1H), 4.09 (s, 1H), 4.02 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 2.88 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.3, 135.9, 135.0, 129.0, 128.8, 128.6, 127.2, 126.8, 126.5, 114.5, 64.9, 62.5, 55.5, 27.1.; IR (neat): ν_{max} 2905, 2836, 1751, 1514, 1249, 744 cm^{-1}.; HRMS (FAB) calcd. for $C_{19}H_{19}NO_2$ (M+H): 294.1495, found 294.1494.



***trans*-1-benzyl-3-(4-methoxyphenyl)-4-phenylazetidin-2-one (2.4i)**[9]

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2i** (97.6 mg, 0.50 mmol) gave **2.4i** (147.8 mg, 86%) as a yellow oil. R_f 0.26 (hexane-EtOAc, 3:1).

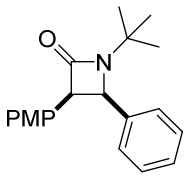
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 3H), 7.33 – 7.26 (m, 5H), 7.19 (d, *J* = 6.0 Hz, 2H), 7.14 – 7.09 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.97 (d, *J* = 14.9 Hz, 1H), 4.28 (d, *J* = 2.2 Hz, 1H), 4.14 (d, *J* = 2.0 Hz, 1H), 3.82 (d, *J* = 14.9 Hz, 1H), 3.78 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 137.5, 135.3, 129.4, 128.9, 126.8, 126.6, 126.4, 122.4, 65.1, 61.4, 27.4.



***trans*-1-isopropyl-3-(4-methoxyphenyl)-4-phenylazetidin-2-one (2.4j)**

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2j** (73.6 mg, 0.50 mmol) gave **2.4j** (84.5 mg, 57%) as a yellow solid. R_f 0.33 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.42 (d, *J* = 2.0 Hz, 1H), 4.04 (d, *J* = 1.7 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.80 (s, 3H), 1.35 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 159.2, 139.4, 129.1, 128.7, 128.7, 127.7, 126.7, 114.5, 63.8, 63.4, 55.5, 45.4, 21.5, 20.9.; IR (neat): ν_{max} 2973, 2838, 1742, 1513, 1247, 699 cm^{-1}.; HRMS (FAB) calcd. for $C_{19}H_{21}NO_2$ (M+H): 296.1651, found 296.1651.

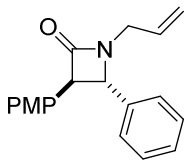


***cis*-1-(*tert*-butyl)-3-(4-methoxyphenyl)-4-phenylazetidin-2-one (2.4k')**

Following the general procedure B, the reaction of alkyne **2.1a** (66.1 mg, 0.50 mmol) with imine **2.2k** (88.7 mg, 0.55 mmol) gave **2.4k'** (12.6 mg, 8%) as a yellow oil. R_f 0.31 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.02 (m, 5H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.5 Hz, 2H), 5.00 (d, *J* = 5.8 Hz, 1H), 4.65 (d, *J* = 5.8 Hz, 1H), 3.67 (s, 3H), 1.34 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 158.4, 137.8, 130.0, 128.1, 127.8, 127.8, 125.5, 113.6, 59.8, 58.5, 55.3, 54.8, 28.5.; IR (neat): ν_{max} 3049, 1740, 1514, 1251, 743 cm^{-1}.; HRMS (FAB) calcd. for $C_{20}H_{23}NO_2$ (M+H):

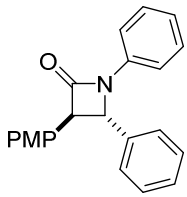
310.1818, found 310.1818.



***trans*-1-allyl-3-(4-methoxyphenyl)-4-phenylazetidin-2-one (2.4l**)

Following the general procedure A, the reaction of alkyne **2.1a** (85.9 mg, 0.65 mmol) with imine **2.2l** (72.6 mg, 0.50 mmol)[9] gave **2.4l** (121.5 mg, 83%) as a yellow oil. R_f 0.35 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.78 (dddd, *J* = 17.1, 10.2, 7.2, 5.2 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 5.12 (d, *J* = 17.0 Hz, 1H), 4.47 (d, *J* = 2.0 Hz, 1H), 4.30 (dd, *J* = 15.5, 5.1 Hz, 1H), 4.13 (s, 1H), 3.80 (s, 3H), 3.41 (dd, *J* = 15.5, 7.2 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.77, 159.27, 137.70, 131.73, 129.26, 128.78, 128.66, 127.34, 126.63, 119.00, 114.51, 64.76, 64.01, 55.48, 43.29.; IR (neat): ν_{max} 2908, 2836, 1751, 1513, 1249, 1179, 1030, 700 cm^{-1}.; HRMS (FAB) calcd. for $C_{19}H_{19}NO_2$ (M+H): 294.1495, found 294.1494.

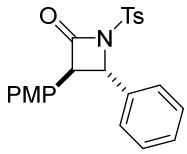


***trans*-3-(4-methoxyphenyl)-1,4-diphenylazetidin-2-one (2.4m**)[10]

Following the general procedure B, the reaction of alkyne **2.1a** (66.1 mg, 0.50 mmol) with imine **2.2l** (65.6 mg, 0.55 mmol) gave **2.4l** (49.8 mg, 32%) as a yellow solid. R_f 0.51 (hexane-EtOAc, 3:1).

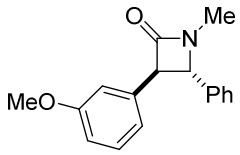
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 7H), 7.30 – 7.24 (m, 4H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.88 (m, 2H), 4.90 (d, *J* = 2.6 Hz, 1H), 4.22 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.5, 137.8,

137.7, 129.5, 129.3, 128.8, 128.8, 127.0, 126.1, 124.2, 117.4, 114.6, 64.8, 64.3, 55.5.



***trans*-3-(4-methoxyphenyl)-4-phenyl-1-tosylazetidin-2-one (2.4n)**

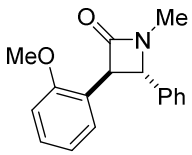
Following the general procedure B, the reaction of alkyne **2.1a** (66.1 mg, 0.50 mmol) with imine **2.2n** (142.6 mg, 0.55 mmol)[11] gave an inseparable mixture of **2.4n** and **2.4n'** (91.0 mg, 45%) as a yellow oil. R_f 0.31 (hexane-EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H, *cis*), 7.72 (d, *J* = 8.3 Hz, 2H, *trans*), 7.59 – 7.49 (m, 4H, *cis*), 7.39 – 7.26 (m, 10H, *trans/cis*), 7.18 – 7.12 (m, 2H, cis), 7.07 – 6.99 (m, 2H, *cis*), 6.98 (d, *J* = 8.7 Hz, 2H, *trans*), 6.83 (d, *J* = 8.7 Hz, 2H, *trans*), 6.81 (dd, *J* = 9.3, 2.5 Hz, 2H, *cis*), 5.66 (d, *J* = 6.8 Hz, 1H, *cis*), 5.09 (d, *J* = 6.8 Hz, 1H, *cis*), 4.92 (d, *J* = 3.4 Hz, 1H, *trans*), 4.21 (d, *J* = 3.3 Hz, 1H, *trans*), 3.88 (d, *J* = 0.9 Hz, 3H, *cis*), 3.79 (s, 3H, *trans*), 2.68 (s, 3H, *cis*), 2.46 (s, 3H, *trans*).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.6, 159.1, 159.8, 145.6, 145.5, 136.2, 135.9, 135.8, 133.6, 130.1, 130.0, 129.9, 129.2, 129.1, 128.7, 128.5, 128.2, 127.9, 127.8, 127.6, 126.7, 124.9, 122.8, 114.7, 113.9, 66.3, 64.0, 62.9, 60.3, 55.5, 55.3, 22.0, 21.9.; IR (neat): ν_{max} 3034, 1793, 1514, 1367, 1169, 735 cm^{-1}.; HRMS (FAB) calcd. for $C_{23}H_{21}NO_4S$ (M+H): 408.1270, found 408.1270.



***trans*-3-(3-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (2.4o)**

Following the general procedure A, the reaction of alkyne **2.1c** (85.9 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4o** (112.5 mg, 84%) as a yellow oil. R_f 0.23 (hexane-EtOAc, 3:1).

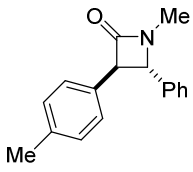
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (m, 4H), 7.30 – 7.25 (m, 2H), 6.90 – 6.82 (m, 3H), 4.46 (d, *J* = 2.2 Hz, 1H), 4.14 (s, 1H), 3.81 (s, 3H), 2.86 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 160.1, 137.5, 136.7, 130.1, 129.3, 128.8, 126.4, 119.8, 113.2, 113.2, 65.8, 65.4, 55.4, 27.2.; IR (neat): ν_{max} 2939, 2835, 1751, 1455, 1048, 698 cm^{-1}.; HRMS (FAB) calcd. for $C_{17}H_{17}NO_2$ (M+H): 268.1338, found 268.1338.



***trans*-3-(2-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (2.4p)**

Following the general procedure A, the reaction of alkyne **2.1d** (85.9 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4p** (126.0 mg, 94%) as a yellow oil. R_f 0.23 (hexane-EtOAc, 3:1).

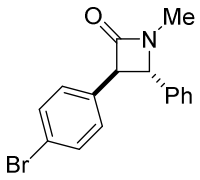
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.24 (m, 7H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 4.43 (d, *J* = 2.2 Hz, 1H), 4.23 (s, 1H), 3.74 (s, 3H), 2.85 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 157.7, 138.5, 129.1, 129.1, 129.0, 128.5, 126.6, 123.9, 120.8, 110.6, 64.4, 62.2, 55.4, 27.4.; IR (neat): ν_{max} 2939, 2837, 1749, 1495, 1248, 755 cm^{-1}.; HRMS (FAB) calcd. for $C_{17}H_{17}NO_2$ (M+H): 268.1338, found 268.1338.



***trans*-1-methyl-1-methyl-4-phenyl-3-(*p*-tolyl)azetidin-2-one (2.4q)**[1]

Following the general procedure A, the reaction of alkyne **2.1e** (75.5 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4q** (109.0 mg, 87%) as a yellow oil. R_f 0.34 (hexane-EtOAc, 3:1).

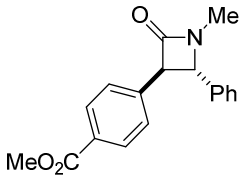
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H), 7.21 – 7.14 (m, 4H), 4.42 (d, *J* = 2.1 Hz, 1H), 4.12 (s, 1H), 2.86 (s, 3H), 2.34 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 137.7, 137.6, 132.2, 129.8, 129.4, 128.8, 127.5, 126.5, 65.8, 65.7, 27.2, 21.4.



***trans*-3-(4-bromophenyl)-1-methyl-4-phenylazetidin-2-one (2.4r)**

Following the general procedure A, the reaction of alkyne **2.1f** (117.7 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4r** (118.0 mg, 75%) as a yellow solid. R_f 0.32 (hexane-EtOAc, 3:1).

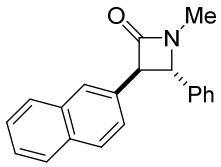
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 5H), 7.32 (dt, *J* = 8.1, 2.6 Hz, 2H), 7.20 – 7.16 (m, 2H), 4.41 (d, *J* = 2.2 Hz, 1H), 4.12 (s, 1H), 2.86 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 137.2, 134.3, 132.2, 129.5, 129.3, 129.1, 126.5, 121.8, 65.4, 65.2, 27.3.; IR (neat): ν_{max} 2907, 1752, 1489, 1388, 1012, 700 cm^{-1}.; HRMS (FAB) calcd. for $C_{16}H_{14}BrNO_2$ (M+H): 316.0337, found 316.0338.



Methyl 4-(*trans*-1-methyl-2-oxo-4-phenylazetidin-3-yl)benzoate (2.4s)[1]

Following the general procedure A, the reaction of alkyne **2.1g** (104.1 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4s** (79.5 mg, 54%) as a yellow solid. R_f 0.18 (hexane-EtOAc, 3:1).

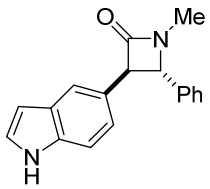
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.49 – 7.32 (m, 7H), 4.47 (d, *J* = 2.1 Hz, 1H), 4.23 (s, 1H), 3.92 (s, 3H), 2.88 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.8, 140.3, 137.1, 130.3, 129.6, 129.4, 129.1, 127.6, 126.4, 65.6, 65.1, 52.3, 27.3.



***trans*-1-methyl-3-(naphthalene-2-yl)-4-phenylazetidin-2-one (2.4t)**[1]

Following the general procedure A, the reaction of alkyne **2.1h** (98.9 mg, 0.65 mmol)[12] with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4t** (129.2 mg, 90%) as a yellow oil. R_f 0.25 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 4H), 7.50 – 7.32 (m, 8H), 4.52 (d, *J* = 2.1 Hz, 1H), 4.33 (s, 1H), 2.90 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.6, 133.6, 132.9, 132.7, 129.4, 128.9, 128.0, 127.9, 126.6, 126.5, 126.2, 125.3, 66.1, 65.6, 27.3.

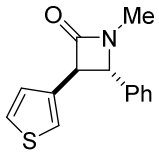


***trans*-3-(1H-indol-5-yl)-1-methyl-4-phenylazetidin-2-one (2.4u)**

Following the general procedure A, the reaction of alkyne **2.1i** (90.0 mg, 0.64 mmol)[13] with imine **2.2a** (58.4 mg, 0.49 mmol) gave **2.4u** (132.3 mg, 96%) as a yellow solid. R_f 0.55 (hexane-EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.57 (s, 1H), 7.46 – 7.40 (m, 2H),

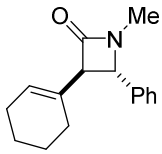
7.38 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 3H), 7.20 (t, *J* = 2.8 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.47 (d, *J* = 1.9 Hz, 1H), 4.25 (s, 1H), 2.90 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 137.9, 135.4, 129.3, 128.7, 128.4, 126.5, 126.5, 125.1, 121.5, 119.7, 111.7, 102.8, 66.5, 27.3.; IR (neat): ν_{max} 3295, 2910, 1732, 1421, 1265, 729 cm^{-1}.; HRMS (FAB) calcd. for $C_{18}H_{16}N_2O$ (M+H): 277.1342, found 277.1341.



***trans*-1-methyl-4-phenyl-3-(thiopen-3-yl)azetidin-2-one (2.4v)**

Following the general procedure A, the reaction of alkyne **2.1j** (70.3 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4v** (90.8 mg, 75%) as a yellow solid. R_f 0.31 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 6H), 7.25 – 7.22 (m, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 4.44 (d, *J* = 2.1 Hz, 1H), 4.21 (s, 1H), 2.85 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 137.5, 135.3, 129.4, 128.9, 126.8, 126.6, 126.4, 122.4, 65.1, 61.4, 27.4.; IR (neat): ν_{max} 2907, 1751, 1386, 1070, 699 cm^{-1}.; HRMS (FAB) calcd. for $C_{14}H_{13}NOS$ (M+H): 244.0797, found 244.0796.

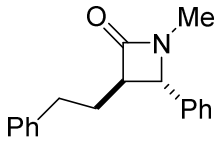


***trans*-3-(cyclohex-1-en-1-yl)-1-methyl-4-phenylazetidin-2-one (2.4w)**

Following the general procedure A, the reaction of alkyne **2.1k** (69.0 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.4w** (98.1 mg, 81%) as a yellow oil. R_f 0.35 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 5.74 – 5.69 (m, 1H), 4.31 (d, *J* = 2.2 Hz, 1H), 3.51 (s, 1H), 2.78 (d, *J* = 0.9 Hz, 3H), 2.06 – 1.98(m, 4H),

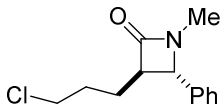
1.72 – 1.64 (m, 2H), 1.64 – 1.56 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 138.2, 131.4, 129.2, 128.6, 126.4, 125.7, 68.4, 62.2, 27.1, 26.6, 25.3, 22.6, 22.3.; IR (neat): ν_{max} 2925, 2834, 1746,1387, 1266, 739, 700 cm^{-1}.; HRMS (FAB) calcd. for $C_{16}H_{19}NO$ (M+H): 242.1546, found 242.1546.



***trans*-1-methyl-3-phenethyl-4-phenylazetidin-2-one (2.4x)**

Following the general procedure B, the reaction of alkyne **2.1l** (65.1 mg, 0.50 mmol) with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4x** (107.2 mg, 81%) as a yellow oil. R_f 0.18 (hexane-EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 3H), 7.26 – 7.14 (m, 5H), 7.13 – 7.07 (m, 2H), 4.14 (d, *J* = 2.0 Hz, 1H), 3.01 (ddd, *J* = 6.3, 5.8, 1.0 Hz, 1H), 2.83-2.69 (m, 5H), 2.20 (ddt, *J* = 13.1, 8.8, 6.7 Hz, 1H), 2.14 – 2.02 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 141.2, 137.9, 129.1, 128.6, 128.5, 126.4, 126.2, 63.2, 60.7, 33.6, 30.8, 27.0.; IR (neat): ν_{max} 3027, 2940, 1745, 1455, 1389, 740, 699 cm^{-1}.; HRMS (FAB) calcd. for $C_{18}H_{19}NO$ (M+H): 266.1546, found 266.1545.

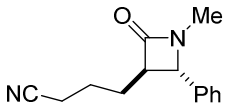


***trans*-3-(3-chloropropyl)-1-methyl-4-phenylazetidin-2-one (2.4y)**

Following the general procedure B, the reaction of alkyne **2.1m** (51.3 mg, 0.50 mmol) with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4y** (73.7 mg, 62%) as a yellow oil. R_f 0.27 (hexane-EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 3H), 7.31 – 7.27 (m, 2H), 4.19 (d, *J* = 2.0 Hz, 1H), 3.54 (t, *J* = 5.9 Hz, 2H), 2.97 (t, *J* = 6.5 Hz, 1H), 2.76 (s, 3H), 2.02 – 1.93 (m, 3H), 1.92 – 1.85 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ

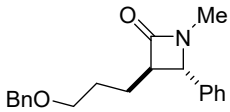
170.07, 137.83, 129.26, 128.69, 126.33, 63.00, 60.58, 44.74, 30.34, 27.08, 26.14.; IR (neat): ν_{max} 2939, 1743, 1456, 1390, 739, 700 cm^{-1}.; HRMS (FAB) calcd. for $C_{13}H_{16}ClNO$ (M+H): 238.0981, found 238.0999.



4-(*trans*-1-methyl-2-oxo-4-phenylazetidin-3-yl)butanenitrile (2.4z)

Following the general procedure B, the reaction of alkyne **2.1n** (46.6 mg, 0.50 mmol) with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4z** (93.8 mg, 82%) as a yellow oil. R_f 0.20 (hexane-EtOAc, 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 3H), 7.31 – 7.27 (m, 2H), 4.18 (d, *J* = 2.0 Hz, 1H), 2.96 (t, *J* = 7.1, 1H), 2.76 (s, 3H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.93 – 1.85 (m, 1H), 1.83 – 1.76 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.63, 137.53, 129.35, 128.85, 126.32, 119.42, 62.86, 60.38, 27.84, 27.14, 23.46, 17.33.; IR (neat): ν_{max} 2936, 2245, 1742, 1456, 1391, 735, 701 cm^{-1}.; HRMS (FAB) calcd. for $C_{14}H_{16}N_2O$ (M+H): 229.1342, found 229.1341.

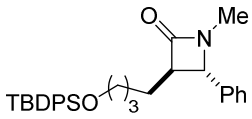


***trans*-3-(3-(benzyoxy)propyl)-1-methyl-4-phenylazetidin-2-one (2.4aa**)

Following the general procedure B, the reaction of alkyne **2.1o** (87.1 mg, 0.50 mmol)[14] with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4aa** (118.2 mg, 76%) as a yellow oil. R_f 0.15 (hexane-EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 10H), 4.47 (s, 2H), 4.16 (d, *J* = 1.9 Hz, 1H), 3.49 – 3.44 (m, 2H), 2.98 (t, *J* = 7.1 Hz, 1H), 2.74 (s, 3H), 1.99 – 1.84 (m, 2H), 1.80 – 1.70 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 138.6, 138.1, 129.1, 128.5, 127.7, 126.3, 73.0, 69.9, 63.0, 61.1, 27.6, 27.0, 25.7.; IR

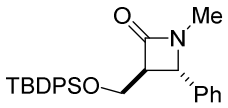
(neat): ν_{max} 2936, 2856, 1746, 1454, 1389, 736, 698 cm^{-1}.; HRMS (FAB) calcd. for $C_{20}H_{23}NO_2$ (M+H): 310.1808, found 310.1807.



***trans*-3-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)-1-methyl-4-phenylazetidin-2-one (2.4ab**)

Following the general procedure B, the reaction of alkyne **2.1p** (168.3 mg, 0.50 mmol)[15] with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4ab** (203.9 mg, 86%) as a yellow oil. R_f 0.42 (hexane-EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H), 7.44 – 7.31 (m, 8H), 7.28 – 7.25 (m, 3H), 4.13 (s, 1H), 3.65 (dd, *J* = 5.5, 3.7 Hz, 2H), 2.98 – 2.91 (m, 1H), 2.75 (s, 3H), 1.92 – 1.67 (m, 2H), 1.59 – 1.47 (m, 4H), 1.04 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.65, 138.22, 135.65, 134.06, 129.68, 129.14, 128.44, 127.73, 126.30, 63.62, 63.10, 61.47, 32.51, 28.65, 27.01, 23.84, 19.35.; IR (neat): ν_{max} 2932, 2857, 1751, 1427, 1110, 738, 700 cm^{-1}.; HRMS (FAB) calcd. for $C_{30}H_{37}NO_2Si$ (M+H): 472.2673, found 472.2672.

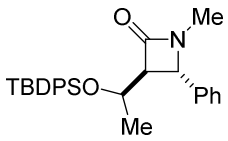


***trans*-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-methyl-4-phenylazetidin-2-one (2.4ac**)

Following the general procedure B, the reaction of alkyne **2.1q** (147.2 mg, 0.50 mmol)[16] with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4ac** (124.8 mg, 58%) as a yellow oil. R_f 0.69 (hexane-EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.47 – 7.32 (m, 8H), 7.26 – 7.22 (m, 3H), 4.53 (d, *J* = 2.1 Hz, 1H), 4.09 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.94 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.81 (s, 3H), 1.07 (s, 9H).; ^{13}C

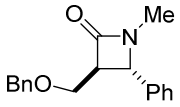
NMR (100 MHz, $CDCl_3$) δ 168.5, 138.3, 135.9, 135.8, 133.6, 133.0, 130.1, 130.0, 129.2, 128.5, 128.0, 128.0, 126.5, 63.2, 59.9, 59.5, 27.2, 27.0, 19.5.; HRMS (FAB) calcd. for $C_{27}H_{31}NO_2Si$ (M+H): 430.2203, found 430.2202.



***trans*-3-(1-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-methyl-4-phenylazetidin-2-one (2.4ad)**

Following the general procedure B, the reaction of alkyne **2.1r** (154.3 mg, 0.50 mmol)[17] with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4ad** (69.5 mg, 31%) as a yellow oil. R_f 0.42 (hexane-EtOAc, 3:1). The diastereoselectivity was determined by the NMR integration of product. The NMR analysis using relative intensity of the product indicated alkyne **2.1r** (26%) and imine **2.2a** (50%) to remain unreacted in the crude mixture.

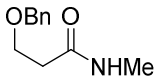
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 12.7, 5.3 Hz, 4H), 7.69 – 7.65 (m, 2H), 7.62 (dd, *J* = 6.7, 1.2 Hz, 2H), 7.47 – 7.28 (m, 19H), 7.13 – 7.06 (m, 2H), 4.68 (s, 1H), 4.41 (s, 1H), 4.38 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.25 (dd, *J* = 6.3, 3.1 Hz, 1H), 3.00 (s, 2H), 2.78 (s, 3H), 2.75 (s, 3H), 1.33 – 1.28 (m, 3H), 1.11 – 0.98 (m, 21H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.3, 138.6, 138.3, 136.3, 136.2, 136.1, 136.0, 134.9, 134.0, 133.8, 133.0, 130.0, 130.0, 129.8, 129.2, 129.1, 128.4, 127.9, 127.9, 127.8, 127.7, 126.7, 126.5, 68.3, 67.7, 66.9, 66.5, 58.4, 58.2, 27.1, 27.1, 27.1, 27.0, 22.5, 21.0, 19.6, 19.5.; IR (neat): ν_{max} 2931, 2857, 1755, 1491, 1382, 1111, 741, 702 cm^{-1}.; HRMS (FAB) calcd. for $C_{28}H_{33}NO_2Si$ (M+H): 434.2360, found 434.2359.



***trans*-3-((benzyoxy)methyl)-1-methyl-4-phenylazetidin-2-one (2.4ae)**

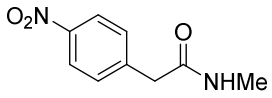
Following the general procedure B, the reaction of alkyne **2.26** (73.1 mg, 0.50 mmol)[18] with imine **2.2a** (65.5 mg, 0.55 mmol) gave **2.4ae** (6.1 mg, 4%) as a yellow oil, along with **2.27** (51.4 mg, 46%) as a yellow oil. R_f 0.18 and 0.03 respectively (hexane-EtOAc, 2:1).

2.4ae - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 10H), 4.58 (q, *J* = 12.1 Hz, 2H), 4.49 (d, *J* = 2.1 Hz, 1H), 3.81 (qd, *J* = 10.5, 4.8 Hz, 2H), 3.22 (d, *J* = 2.9 Hz, 1H), 2.78 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.2, 138.0, 129.2, 128.6, 128.6, 127.9, 127.8, 126.5, 73.4, 66.2, 61.4, 60.1, 27.2.; IR (neat): ν_{max} 3033, 2859, 1754, 1455, 1118, 739, 699 cm^{-1}.; HRMS (FAB) calcd. for $C_{18}H_{19}NO_2$ (M+H): 282.1495, found 282.1494.



3-(benzyloxy)-N-methylpropanamide (**2.39**)

2.39 - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 6.31 (s, 1H), 4.53 (s, 2H), 3.73 (t, *J* = 5.8 Hz, 2H), 2.78 (d, *J* = 4.9 Hz, 3H), 2.48 (t, *J* = 5.8 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.9, 132.2, 128.7, 128.0, 73.4, 66.5, 37.1, 26.3.; IR (neat): ν_{max} 3302, 3062, 2866, 1649, 1599, 1199, 1119, 736, 698 cm^{-1}.; HRMS (FAB) calcd. for $C_{11}H_{15}NO_2$ (M+H): 194.1182, found 194.1181.



***N*-methyl-2-(4-nitrophenyl)acetamide** (**2.41**)[19]

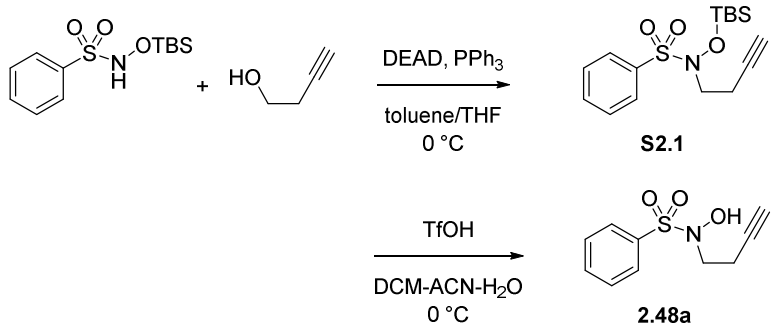
Following the general procedure A, the reaction of alkyne **2.40** (73.6 mg, 0.65 mmol) with imine **2.2a** (59.6 mg, 0.50 mmol) gave **2.41** (21.1 mg, 15%) as a white solid (R_f 0.16, EtOAc only), and unreacted alkyne **2.40** (11.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 5.42 (s, 1H), 3.65 (s, 2H), 2.82 (d, *J* = 4.9 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9. 147.4, 142.6, 130.4, 124.1, 43.4, 26.9.

2.4.2.2 Ruthenium-Catalyzed Reconstitution

Preparation of *N*-sulfonyl-*N*-hydroxylamines

N-Sulfonyl-*N*-hydroxylamines **2.48a**, **2.48b**, **2.48c**, **2.48d**, **2.48g**, **2.48h**, **2.48e** and **2.48f** were prepared according to literatures.[20,21] **2.48i**, **2.48j**, and **2.48k** were synthesized using analogous procedure for the synthesis of **2.48a**.

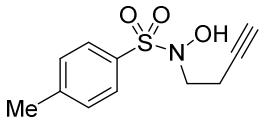


***N*-(but-3-yn-1-yl)-*N*-hydroxybenzenesulfonamide (2.48a)**[20]

To a solution of *N*-benzenesulfonyl-*O*-(tert-butyldimethylsilyl)hydroxylamine (1.50 g, 5.2 mmol),[20] 3-buyn-1-ol (0.43 mL, 5.7 mmol), and PPh_3 (2.74 g, 10.4 mmol) in toluene/THF (21 mL, 3:1) was added diethylazodicarboxylate (1.23 mL, 7.8 mmol) slowly at 0 °C. After 1 h, the mixture was poured into EtOAc, and washed with H_2O and dried over anhydrous $MgSO_4$. Concentration followed by column chromatography on SiO_2 gave **S2.1** (1.66g, 94%) as a viscous oil.

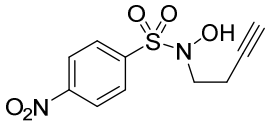
To a solution of *O*-silylhydroxylamine **S2.1** (1.5 g, 5.2 mmol) in water-saturated DCM/ACN (24 mL, 1:1) was added TfOH (0.78, 8.8 mmol) slowly at 0 °C. After 1 h, the reaction was quenched and neutralized by adding saturated $NaHCO_3$(aq). The aqueous layer was extracted with DCM and combined organic phase was dried over anhydrous $MgSO_4$, and concentrated in vacuo. Column chromatography on SiO_2 afforded title compound **2.48a** (965.8 mg, 97%) as white crystal.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 2H), 6.39 (s, 1H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.54 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 132.5, 129.9, 129.2, 80.6, 70.4, 51.5, 17.5.



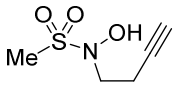
***N*-(but-3-yn-1-yl)-*N*-hydroxy-4-methylbenzenesulfonamide (2.48b)**[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 6.29 (s, 1H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.46 (s, 3H), 2.53 (td, *J* = 7.3 Hz, 2.6 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 129.9, 129.8, 129.3, 80.8, 70.3, 51.6, 21.9, 17.4.



***N*-(but-3-yn-1-yl)-*N*-hydroxy-4-nitrobenzenesulfonamide (2.48c)**[20]

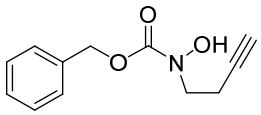
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.46 (d, *J* = 8.9 Hz, 2H), 8.09 (d, *J* = 8.9 Hz, 2H), 2.98 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 2.6 Hz, 1H), 2.40 (td, *J* = 6.7 Hz, 2.6 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 137.9, 130.9, 124.3, 81.4, 51.9, 16.4.



***N*-(but-3-yn-1-yl)-*N*-hydroxy-4-methylsulfonamide (2.45d)**[20]

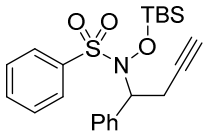
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (br s, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 2.95 (s, 3H), 2.61 (td, *J* = 7.0, 2.3 Hz, 2H), 2.04 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (100

MHz, $CDCl_3$) δ 80.6, 70.5, 51.4, 31.5, 17.7.



benzyl but-3-yn-1-yl(hydroxy)carbamate (**2.45e**)

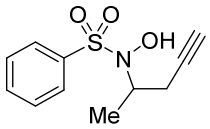
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 5.17 (s, 2H), 3.73 (t, *J* = 7.0 Hz, 2H), 2.53 (td, *J* = 7.0, 2.5 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 128.8, 128.6, 128.4, 81.2, 70.2, 68.3, 49.2, 17.2.; IR (neat): ν_{max} 3288, 2942, 1701, 1455, 1359, 1215, 1108, 1027, 739 cm^{-1}.



***N*-((*tert*-butyldimethylsilyl)oxy)-*N*-(1-phenylbut-3-yn-1-yl)benzenesulfonamide** (**S2.2**)[20]

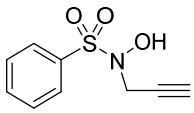
S2.2 was prepared in analogous manner to **S2.1**. Free hydroxylamine **2.48g** was obtained on treatment of TfOH in wet DCM/CAN and directly used after workup due to unstable nature of **2.48g**.

S2.2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.63 – 7.56 (m, 1H), 7.50 – 7.43 (m, 2H), 7.39 (dd, *J* = 7.2, 1.9 Hz, 2H), 7.27 – 7.19 (m, 3H), 5.07 (dd, *J* = 10.5, 3.9 Hz, 1H), 2.65 (ddd, *J* = 17.2, 10.5, 2.6 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.90 (t, *J* = 2.7 Hz, 1H), 0.89 (s, 9H), 0.29 (s, 3H), -0.26 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.7, 133.1, 129.0, 128.6, 128.4, 128.1, 80.7, 70.8, 63.6, 25.7, 23.0, 18.1, -2.9, -3.6.



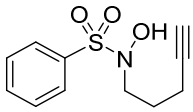
***N*-hydroxy-*N*-(pent-4-yn-2-yl)benzenesulfonamide** (**2.48h**)[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 6.35 (s, 1H), 4.17 – 4.05 (m, 1H), 2.40 – 2.25 (m, 2H), 2.01 (s, 1H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 134.0, 129.3, 129.2, 81.0, 70.7, 55.8, 24.3, 15.1.



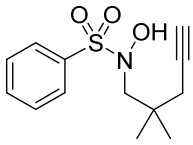
***N*-hydroxy-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**2.48i**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 2H), 6.96 (s, 1H), 3.94 (s, 2H), 2.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 132.7, 130.1, 129.2, 75.8, 74.0, 43.3.; IR (neat): ν_{max} 3391, 3059, 1336, 1174, 1063, 890, 753 cm^{-1}.



***N*-hydroxy-*N*-(pent-4-yn-1-yl)benzenesulfonamide** (**2.48j**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 6.33 (s, 1H), 3.03 (t, *J* = 6.7Hz, 2H), 2.30 (td, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.85 (p, *J* = 6.8 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 132.4, 129.9, 129.1, 83.5, 69.3, 51.6, 25.8, 15.9.; IR (neat): ν_{max} 3293, 2940, 2118, 1447, 1345, 1170, 1069, 735 cm^{-1}.



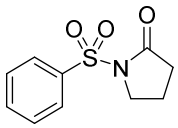
***N*-(2,2-dimethylpent-4-yn-1-yl)- *N*-hydroxybenzenesulfonamide** (**2.48k**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.1 Hz, 2H), 7.69 (t, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 2.88 (s, 2H), 2.22 (s, 2H), 2.00 (s, 1H),

1.08 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 133.4, 129.7, 129.1, 81.9, 70.6, 61.9, 34.9, 30.3, 25.6.; IR (neat): ν_{max} 3300, 2966, 2116, 1447, 1336, 1169, 1090, 748 cm^{-1}.

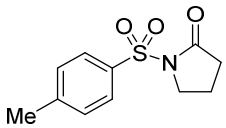
General Procedure C: Reconstitutive Lactam Synthesis

To a flame-dried vial equipped with a screw cap were added *N*-sulfonyl-*N*-hydroxylaminoalkyne, (1.0 mmol, 1.0 equiv), $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol, 5 mol%), and DMF (10 mL, 0.1 M). After sealing the tube with a screw cap, the resulting orange solution was heated at 100 °C. Upon complete consumption of the starting alkynes, the reaction mixture was cooled to ambient temperature. The crude mixture is poured into water, and extracted with diethyl ether three times. Combined organic layer was washed by brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on a silica gel afforded lactam product in an analytically pure form.



1-(phenylsulfonyl)pyrrolidine-2-one (2.57a)[22]

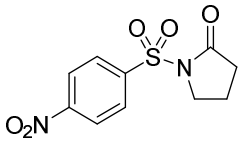
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 3.92 (t, *J* = 8.2 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 2,14 – 2.04 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 138.2, 134.2, 129.2, 128.1, 47.4, 32.3, 18.3.



1-((4-methylphenyl)sulfonyl)pyrrolidine-2-one (2.57b)[23]

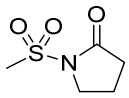
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz,

2H), 3.90 (t, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 2.43 (t, *J* = 8.1 Hz, 2H), 2,13 – 2.01 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 145.4, 135.4, 129.9, 128.3, 47.5, 32.5, 21.9, 18.4.



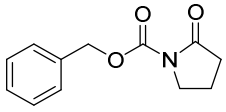
1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-one (2.57c)[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 10.7 Hz, 2H), 3.95 (t, *J* = 7.1 Hz, 2H), 2.48 (t, *J* = 8.1 Hz, 2H), 2,18 – 2.01 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 143.6, 129.8, 124.5, 47.6, 32.2, 18.5.



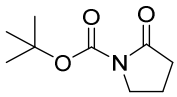
1-(methylsulfonyl)pyrrolidine-2-one (2.57d)[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, *J* = 7.0 Hz, 2H), 3.26 (s, 3H), 2.57 (t, *J* = 8.1 Hz, 2H), 2,21 – 2.08 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 46.8, 40.7, 32.4, 18.5.



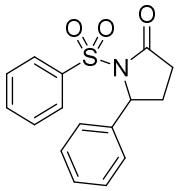
benzyl 2-oxopyrrolidine-1-carboxylate (2.57e)[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.40 – 7.29 (m, 3H), 5.28 (s, 2H), 3.91 – 3.73 (m, 2H), 2.54 (t, *J* = 8.1 Hz, 2H), 2.03 (tt, *J* = 8.0, 7.7 Hz, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 151.7, 135.6, 128.8, 128.6, 128.4, 68.2, 46.6, 33.0, 17.8.



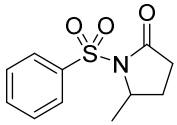
***tert*-butyl 2-oxopyrrolidine-1-carboxylate (2.57f)**[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (t, *J* = 7.1 Hz, 2H), 2.51 (t, *J* = 8.1 Hz, 2H), 2.04 – 1.95 (m, 2H), 1.53 (s, 9H).



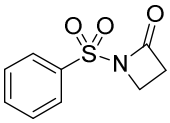
5-phenyl-1-(phenylsulfonyl)pyrrolidine-2-one (2.57g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.59 – 7.52 (m, 1H), 7.42 – 7.33 (m, 2H), 7.31 – 7.22 (m, 3H), 7.14 – 7.07 (m, 2H), 5.47 (d, 1H), 2.77 – 2.46 (m, 3H), 2.02 – 1.94 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 140.6, 138.6, 133.9, 129.0, 128.7, 128.5, 126.2, 63.2, 30.8, 28.4.; IR (neat): ν_{max} 3065, 2967, 1951, 1737, 1448, 1360, 1169, 1089, 954, 725 cm^{-1}.



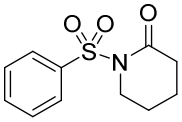
5-methyl-1-(phenylsulfonyl)pyrrolidine-2-one (2.57h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.61 – 4.48 (m, 1H), 2.64 – 2.50 (m, 1H), 2,43 – 2.21 (m, 2H), 1.79 – 1.67 (m, 1H), 1.47 (d, *J* = 6.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 139.1, 134.0, 129.0, 128.3, 56.6, 30.7, 26.8, 21.6.; IR (neat): ν_{max} 3068, 2978, 1902, 1732, 1448, 1355, 1168, 1089, 956, 733 cm^{-1}.



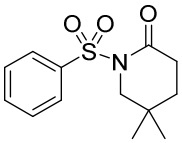
1-(phenylsulfonyl)azetidin-2-one (2.57j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 5.1 Hz, 2H), 3.05 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 138.5, 134.4, 129.7, 127.5, 40.3, 37.1.



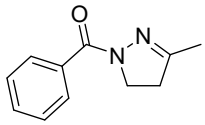
1-(phenylsulfonyl)piperidin-2-one (2.57k)[25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 3.91 (t, *J* = 9.4 Hz, 2H), 2.41 (t, *J* = 6.7 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.82 – 1.73 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 139.2, 133.8, 128.8, 128.7, 47.2, 34.3, 23.5, 20.5.



5,5-dimethyl-1-(phenylsulfonyl)piperidin-2-one (2.57l)

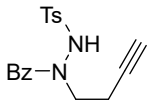
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.1 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 3.62 (s, 2H), 2.40 (td, *J* = 7.1, 2.3 Hz, 2H), 1.57 (td, *J* = 7.2, 1.8 Hz, 2H), 1.06 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 139.1, 133.8, 128.8, 128.7, 57.5, 33.6, 31.3, 30.7, 25.9.; IR (neat): ν_{max} 3059, 2963, 1972, 1683, 1449, 1344, 1167, 1087, 920, 750 cm^{-1}.



1-benzoyl-3-methyl-4,5-dihydropyrazole (2.63a)[26]

In a similar way to general procedure C, **2.63a** was prepared from corresponding hydrazine. To a screw-cap vial were added *N*-benzoyl-*N*-(but-1-yn-4-yl)hydrazine (18.8 mg, 0.1 mmol) and $CpRu(PPh_3)_2Cl$ (7.3 mg, 0.01 mmol), and MeCN (1.0 mL, 0.1 M) in this order. The solution was bubbled with argon gas for approximately 30 seconds, and sealed with a screw-cap. Resulting orange solution was stirred at 80 °C for 1 day. After evaporation of volatile materials, the crude mixture was directly subjected to column chromatography on SiO_2, from which dihydropyrazole **2.63a** was isolated. (15.9 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.3 Hz, 2H), 7.45 – 7.33 (m, 3H), 4.07 (t, *J* = 9.8 Hz, 2H), 2.83 (t, *J* = 9.9 Hz, 2H), 2.03 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 166.4, 157.9, 130.5, 129.4, 127.6, 44.7, 35.1, 16.2.

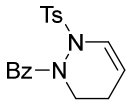


***N′*-benzoyl-*N′*-(but-3-yn-1-yl)-4-methylbenzenesulfonohydrazide (2.60b)**

To a solution of *N*-benzoyl-*N*-(but-1-yn-4-yl)hydrazine (376.5 mg, 2.0 mmol) and pyridine (0.40 mL, 5.0 mmol) in DCM (20 mL) was added *p*-toluenesulfonyl chloride (400.4 mg, 2.1 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred for 6 hours at ambient temperature. After starting materials were consumed fully, crude mixture was poured into water, and aqueous layer was extracted with DCM three times. Combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure.

Column chromatography on SiO_2 gave tosylhydrazied **2.60b** (632.5 mg, 92%) as a yellow gum.

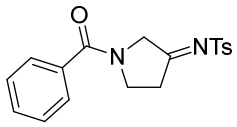
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.81 (br s, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 6.3 Hz, 2H), 7.31 – 7.18 (m, 4H), 3.88 (br s, 2H), 2.52 (br s, 2H), 2.32 (s, 3H), 1.91 (s, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.94, 144.95, 133.23, 132.36, 131.30, 129.55, 128.51, 128.41, 128.36, 80.18, 71.35, 50.63, 21.64, 17.04.; IR (neat): ν_{max} 3290, 1656, 1378, 1340, 1165, 737, 698 cm^{-1}.



2-benzoyl-1-((4-methylphenyl)sulfonyl)-1,2,3,4-tetrahydropyridazine (2.66b)

To a screw-cap vial were added **2.60b** (34.2 mg, 0.1 mmol) and CpRu(naphthalene)PF_6 (4.4 mg, 0.01 mmol), *i*Pr-AZARYPHOS (9.3 mg, 0.02 mmol),[27] and MeCN (1.0 mL). The solution was bubbled with argon gas for approximately 30 seconds, and sealed with a screw-cap. Resulting orange solution was stirred at 80 °C for 1 day. After evaporation of volatile materials, the crude mixture was directly subjected to column chromatography on SiO_2, from which dihydropyrazole **2.66b** (24.9 mg, 71%) and **2.67b** were isolated (5.6 mg, 16%).

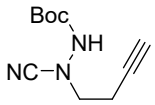
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.46 – 7.24 (m, 5H), 7.28 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.53 (t, *J* = 6.8 Hz, 1H), 4.40 (br s, 1H), 2.43 (s, 3H), 2.36 – 2.12 (m, 2H), 1.85 (dt, *J* = 14.0, 7.2 Hz, 1H).; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 171.7, 145.5, 134.6, 132.2, 130.2, 129.9, 128.6, 127.7, 127.6, 125.3, 113.5, 38.2, 21.8, 21.4.; IR (neat): ν_{max} 3027, 1666, 1373, 1274, 1171, 759, 713 cm^{-1}.



Partial Characterization of

***N*-(1-benzoylpyrrolidin-3-ylidene)-4-methylbenzenesulfonamide (2.67b)**

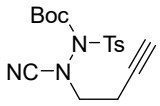
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 2.4 Hz, 2H), 7.44 – 7.33 (m, 7H), 4.15 – 4.02 (m, 4H), 3.12 (t, *J* = 9.0 Hz, 2H), 2.45 (s, 3H).



***tert*-butyl 2-(but-3-yn-1-yl)-2-cyanohydrazine-1-carboxylate (S2.3)**

To a solution of *N'*-(but-1-yn-4-yl)-*tert*-butylcarbazate (604.1 mg, 3.28 mmol) in THF (6.5 mL) was added trimethylsilylisocyante (0.47 mL, 3.3 mmol) at 0 ^{o}C under nitrogen atmosphere. After stirring for 1 h at this temperature, MeOH (3.3 mL) was added to the mixture. The mixture was then stirred at 55 ^{o}C for 2 h before all volatiles were removed under reduced pressure. After crude mixture was re-dissolved in pyridine (6.5 mL), TsCl was added to the mixture at 0 ^{o}C. After 26 h, the mixture was poured into water, and aqueous layer was extracted with DCM three times. Combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography on SiO_2 gave **S2.3** (872.9 mg, 99%) as a white amorphous solid. R_f 0.73 (hexane-EtOAc 7:3)

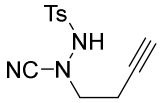
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 3.46 (t, *J* = 6.8 Hz, 2H), 2.51 (td, *J* = 6.9, 2.6 Hz, 2H), 2.04 (t, *J* = 2.5 Hz, 1H), 1.47 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 114.2, 79.6, 70.9, 54.1, 29.6, 28.1, 17.3.; IR (neat): ν_{max} 3299, 2979, 2925, 2225, 1731, 1495, 1371, 1159 cm^{-1}.



***tert*-butyl 2-(but-3-yn-1-yl)-2-cyano-1-tosylhydrazine-1-carboxylate (S2.4)**

To a solution of **S2.3** (366.2 mg, 1.75 mmol) in THF (17.5 mL) was added NaH (77.2 mg, 1.93 mmol) at 0 °C under nitrogen atmosphere. After 30 min, TsCl (400.4 mg, 2.1 mmol) was added to the mixture. The mixture was then stirred at ambient temperature for 17 h at which time all the starting materials were consumed. The mixture was diluted with Et_2O, washed with water and brine, dried over $MgSO_4$. Combined organic layers were concentrated under reduced pressure and subjected to column chromatography on SiO_2 affording **S2.4** (452.5 mg, 71%) as a white amorphous solid. R_f 0.23 (hexane-EtOAc 85:15)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.31 (dt, *J* = 5.3, 2.6 Hz, 2H), 3.70 – 3.60 (m, 2H), 2.63 (td, *J* = 7.6, 2.4 Hz, 2H), 2.40 (s, 3H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.39 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 146.1, 134.3, 129.8, 128.7, 112.0, 87.4, 79.0, 71.0, 55.8, 27.8, 21.7, 17.5.



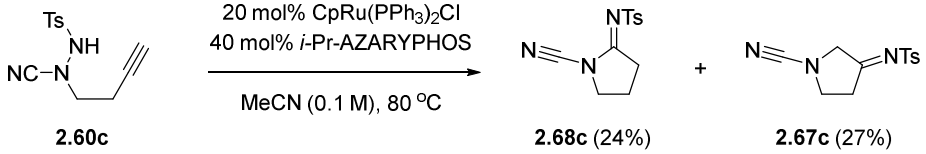
Experimental Procedure and Partial Characterization of

***N'*-(but-3-yn-1-yl)-*N'*-cyano-4-methylbenzenesulfonohydrazide (2.60c)**

To a solution of **S2.4** (470.8 mg, 1.3 mmol) in MeCN (13 mL) was added TMSI (0.41 mg, 2.86 mmol) at 0 °C under nitrogen atmosphere. After stirring at ambient temperature for 75 min, TBAF solution (4.5 mL, 1 M in THF) was added to the mixture. After stirring at ambient temperature for 6 hours, the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was diluted with Et_2O, washed with water and brine, dried over $MgSO_4$. Combined

organic layers were concentrated under reduced pressure and subjected to column chromatography on SiO_2 affording **2.60c** (206.7 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.39 (dd, *J* = 9.4, 8.8 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.58 (td, *J* = 6.4, 2.8 Hz, 2H) 2.45 (s, 3H), 2.10 (t, *J* = 2.4 Hz, 1H).



2.60c **2.68c** (24%) **2.67c** (27%)

***Experimental Procedure and Partial Characterization of* (*E*)-*N*-(1-cyanopyrrolidin-2-ylidene)-4-methylbenzenesulfonamide (2.68c) and (*E*)-*N*-(1-cyanopyrrolidin-3-ylidene)-4-methylbenzenesulfonamide (2.67c)**

To a screw-cap vial were placed **2.60c** (26.3 mg, 0.10 mmol), CpRu(naphthalene)PF_6 (8.8 mg, 0.02 mmol), *i*Pr-AZARYPHOS (18.6 mg, 0.04 mmol) and MeCN (2.0 mL). The solution was thoroughly bubbled with argon gas before tightly sealed and heated to 70 °C. After stirring for 7 hours, solvent was evaporated and Crude ^{1}H NMR was taken. Column chromatography on SiO_2 afforded inseparable mixture of **2.68c**, **2.67c**, and *i*-Pr-AZARYPHOS (24.0 mg, ratio of 1:1.15:0.93), among which spectra of the AZARYPHOS ligand is known. Two major products **2.68c** and **2.67c** were assigned ambiguously on the basis of ^{1}H NMR and gCOSY of the mixture. R_f 0.50 (hexane-EtOAc 1:1)

2.68c ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.83 (t, *J* = 7.3 Hz, 2H), 3.20 (t, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 2.35 – 2.22 (m, 2H).

2.67c ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1Hz, 2H), 7.38 (d, *J* = 8.1

Hz, 2H), 4.11 (s, 2H), 3.91 (t, *J* = 10.1 Hz, 2H), 3.12 (t, *J* = 10.0 Hz, 2H), 2.46 (s, 3H).

2.4.2.3. Ruthenium-Catalyzed Amidation

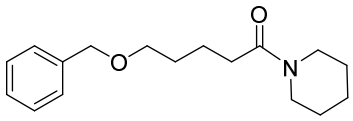
General Procedure D: Amidation Reaction of Terminal Alkynes Using HOBt

To a 5 mL volume of glass vial equipped with a screw-cap were added an alkyne (0.5 mmol, 1.0 equiv), an amine (0.55 mmol, 1.1 equiv), 1-hydroxybenzotriazole (74.3 mg, 0.55 mmol, 1.1 equiv), $CpRu(PPh_3)_2Cl$ (18.1 mg, 0.025 mmol, 0.05 equiv) and *t*-BuOH (1.25 ml, 0.4 M) in this order. When amine hydrochloride salt was used as an amine source, $NaHCO_3$ (0.10 mmol, 2.0 equiv) was added. The solution was bubbled with argon gas for approximately 10-20 seconds before closing screw-cap. The reaction was stirred at 80 ^oC until TLC monitoring indicated that the alkyne was fully consumed. The mixture was cooled down to ambient temperature and diluted with ethyl acetate (10 mL). The organic phase was washed with sat. $K_2CO_{3(aq)}$ solution three times (5 mL each), dried ($MgSO_4$), filtered on silica gel, and evaporated. The crude product was further purified by flash column chromatography on SiO_2 to afford an amide.

General Procedure E: Ester Synthesis from Terminal Alkynes Using HOBt

To a 5 mL volume of glass vial equipped with a screw-cap were added an alkyne (0.5 mmol, 1.0 equiv), an alcohol (0.55 mmol, 1.1 equiv), 1-hydroxybenzotriazole (74.3 mg, 0.55 mmol, 1.1 equiv), $CpRu(PPh_3)_2Cl$ (18.1 mg, 0.025 mmol, 0.05 equiv), DMAP (6.1 mg, 0.05 mmol, 10 mol%) and toluene (1.25 ml, 0.4 M) in this order. The solution was bubbled with argon gas for approximately 10-20 seconds before closing screw-cap. The reaction was stirred at 80 ^oC until TLC monitoring indicated that the alkyne was fully consumed. The mixture was cooled down to ambient temperature and diluted

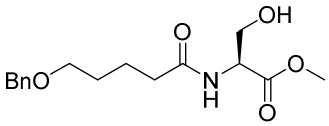
with ethyl acetate (10 mL). The organic phase was washed with sat. $K_2CO_{3(aq)}$ solution three times (5 mL each), dried ($MgSO_4$), filtered on silica gel, and evaporated. The crude product was further purified by flash column chromatography on SiO_2 to afford an ester.



5-(benzyloxy)-1-(piperidin-1-yl)pentan-1-one (2.81a)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (17.4 mg, 0.1 mmol)[28] and piperidine (10.9 μL, 0.11 mmol), the reaction was heated at 80 ^oC for 1 hour. **2.81a** was obtained as a yellow oil.

^1H NMR (300MHz, $CDCl_3$): δ 7.40 – 7.17 (m, 5H), 4.49 (s, 2H), 3.58 – 3.44 (m, 4H), 3.42 – 3.30 (m, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.76 – 1.45 (m, 10H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.39, 138.68, 128.45, 127.74, 127.61, 73.00, 70.21, 46.81, 42.76, 33.20, 29.55, 26.66, 25.70, 24.68, 22.37.; HRMS (ESI) calcd. for $C_{17}H_{25}NO_2Na$ $[M+Na]^+$: 298.1777, found: 298.1780.

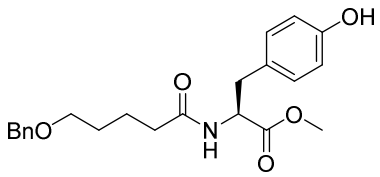


methyl (5-(benzyloxy)pentanoyl)-*L*-serinate (2.81b)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and *L*-Serine methyl ester hydrochloride (85.6 mg, 0.55 mmol), the reaction was heated at 80 ^oC for 24 hours. Amide **2.81b** (132.1 mg, 85%) was obtained as a yellow oil. R_f 0.46 (EtOAc).

^1H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.09 (m, 5H), 6.77 (d, *J* = 7.7 Hz, 1H), 4.59 – 4.47 (m, 1H), 4.39 (s, 2H), 3.83 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.64 (s, 3H), 3.39 (t, *J* = 6.0 Hz, 2H), 2.18 (t, *J* = 7.1 Hz, 2H), 1.61

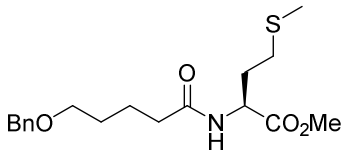
(ddd, *J* = 19.0, 10.5, 4.9 Hz, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.69, 171.15, 138.39, 128.43, 127.76, 127.66, 72.98, 70.02, 62.89, 54.65, 52.58, 35.99, 29.02, 22.55.; HRMS (ESI) calcd. for $C_{16}H_{23}NO_5Na$ $[M+Na]^+$: 332.1468, found: 332.1468.



methyl (5-(benzyloxy)pentanoyl)-*L*-tyrosinate (2.81c)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and *L*-Tyrosine methyl ester hydrochloride (127.4 mg, 0.55 mmol), the reaction was heated at 80 °C for 24 hours. **2.81c** (191.7 mg, 99%) was obtained as a yellow oil. R_f 0.26 (hexane-EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 6.7 Hz, 1H), 7.39 – 7.12 (m, 5H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 8.0 Hz, 1H), 4.81 (dd, *J* = 13.8, 6.3 Hz, 1H), 4.45 (s, 2H), 3.66 (s, 3H), 3.43 (t, *J* = 6.0 Hz, 2H), 3.02 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.89 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.18 (t, *J* = 7.2 Hz, 2H), 1.77 – 1.41 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.51, 172.37, 155.90, 138.27, 130.19, 128.42, 127.78, 127.67, 126.73, 115.65, 72.92, 69.92, 53.41, 52.36, 37.05, 35.94, 28.79, 22.52.; HRMS (ESI) calcd. for $C_{22}H_{27}NO_5Na$ $[M+Na]^+$: 408.1781, found: 408.1780.

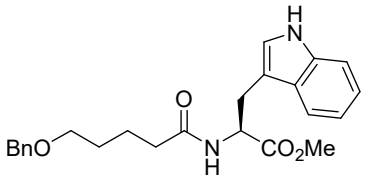


methyl (5-(benzyloxy)pentanoyl)-*L*-methioninate (2.81d)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and *L*-methionine methyl ester hydrochloride (109.8 mg, 0.55 mmol),

the reaction was heated at 80 °C for 24 hours. **2.81d** (160.9 mg, 86%) was obtained as a yellow oil. R_f 0.34 (hexane-EtOAc 1:1)

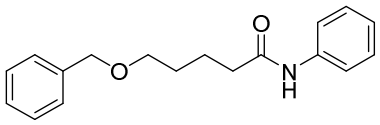
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H), 6.30 (br d, *J* = 7.5 Hz, 1H), 4.70 (td, *J* = 7.5, 5.3 Hz, 1H), 4.49 (s, 2H), 3.74 (s, 3H), 3.50 (t, *J* = 6.0 Hz, 2H), 2.49 (dd, *J* = 11.0, 4.3 Hz, 2H), 2.27 (t, *J* = 7.2 Hz, 2H), 2.19 – 2.08 (m, 1H), 2.07 (s, 3H), 1.92 (td, *J* = 14.3, 7.4 Hz, 1H), 1.80 – 1.60 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.93, 172.70, 138.57, 128.54, 127.85, 127.74, 73.14, 70.23, 52.60, 51.56, 36.25, 31.81, 30.15, 29.10, 22.80, 15.61.; HRMS (ESI) calcd. for $C_{18}H_{27}NO_4SNa$ $[M+Na]^+$: 376.1553, found: 376.1552.



methyl (5-(benzyloxy)pentanoyl)-*L*-tryptophanate (2.81e)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and *L*-tryptophan methyl ester hydrochloride (140.1 mg, 0.55 mmol), the reaction was heated at 80 °C for 11 hours. **2.81e** (167.5 mg, 82%) was obtained as a yellow oil. R_f 0.31 (hexane-EtOAc 1:1)

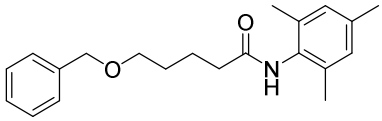
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.11 (m, 6H), 7.04 (t, *J* = 7.1 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.09 (d, J = 7.8 Hz, 1H), 4.83 (m, 1H), 4.33 (s, 2H), 3.52 (s, 3H), 3.30 (t, *J* = 6.1 Hz, 2H), 3.24 – 2.99 (m, 2H), 2.02 (t, *J* = 7.2 Hz, 2H), 1.66 – 1.34 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.88, 172.59, 138.50, 136.27, 128.44, 127.75, 127.65, 127.64, 123.06, 122.05, 119.48, 118.42, 111.49, 109.63, 72.92, 70.00, 53.02, 52.32, 36.06, 29.02, 27.64, 22.43.; HRMS (ESI) calcd. for $C_{24}H_{28}N_2O_4Na$ $[M+Na]^+$: 431.1941, found: 431.1941.



5-(benzyloxy)-*N*-phenylpentanamide (2.81f)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and aniline (50.1 μL, 0.55 mmol), the reaction was heated at 80 °C for 1 h. Anilide **2.81f** (131.8 mg, 93%) was obtained as a yellow oil. R_f 0.61 (hexane-EtOAc, 1:1)

^{1}H NMR (500MHz, $CDCl_3$): δ 7.95 – 7.85 (brs, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 4.3 Hz, 3H), 7.30 – 7.26 (m, 1H), 7.26 – 7.20 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.48 (s, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.72 – 1.63 (m, 2H).; ^{13}C NMR (125 MHz, CDCl3) δ 171.58, 138.28, 138.14, 128.86, 128.50, 127.89, 127.76, 124.01, 119.82, 73.20, 70.52, 37.26, 28.75, 23.15.; HRMS (ESI) calcd. for $C_{18}H_{21}NO_2Na$ $[M+Na]^+$: 306.1464, found: 306.1467.

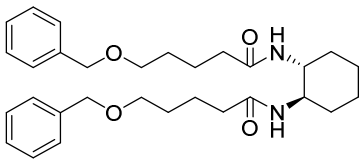


5-(benzyloxy)-*N*-mesitylpentanamide (2.81g)

Following the general procedure D with additional DMAP (12.2 mg, 0.1 mmol), 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and 2,4,6-trimethylaniline (77.2 μL, 0.55 mmol) were used and the reaction was heated at 80 °C for 5 hours. **2.81g** (131.8 mg, 81%) was obtained as a yellow oil. R_f 0.57 (hexane-EtOAc 1:1)

^{1}H NMR (300MHz, $CDCl_3$): δ7.36 – 7.19 (m, 5H), 6.88 (s, 2H), 6.73 (s, 1H), 4.51 (s, 2H), 3.55 (t, *J* = 6.1 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 2.15 (s, 6H), 1.95 – 1.69 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.75, 138.57,

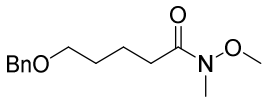
136.81, 135.26, 131.51, 129.40, 128.92, 128.52, 127.83, 73.12, 70.20, 36.37, 29.35, 23.15, 21.05, 18.47.; HRMS (ESI) calcd. for $C_{21}H_{27}NO_2Na$ $[M+Na]^+$: 308.1934, found: 308.1936.



***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(5-(benzyloxy)pentanamide) (2.81h)**

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and (±)-*trans*-diaminocyclohexane (33 μL, 0.275 mmol), the reaction was heated at 80 °C for 4 hours. **2.81h** (97.0 mg, 78%) was obtained as a yellow oil. R_f 0.17 (hexane-EtOAc 2:1)

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 – 7.10 (m, 10H), 6.13 (d, *J* = 5.6Hz, 2H), 4.47 (s, 4H), 3.65 – 3.10 (m, 2H), 3.46 (t, *J* = 4.8Hz, 4H), 2.14 (t, *J* = 6.0 Hz, 4H), 1.96 (d, *J* = 10.8 Hz, 2H), 1.75 – 1.57 (m, 10H), 1.32 – 1.19 (m, 2H), 1.19 – 1.10 (m, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.74, 138.63, 128.57, 127.89, 127.75, 73.17, 70.30, 53.82, 36.62, 32.43, 29.21, 24.84, 22.95.; HRMS (ESI) calcd. for $C_{30}H_{42}N_2O_4Na$ $[M+Na]^+$: 517.3037, found: 517.3035.

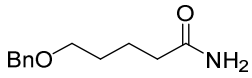


5-(benzyloxy)-*N*-methoxy-*N*-methylpentanamide (2.81i)

Following the general procedure D without an amine source, the reaction was heated at 80 °C for 1 h using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) as an alkyne. After the mixture was cooled down to ambient temperature, *N*,*O*-dimethylhydroxylamine hydrochloride (53.6 mg, 0.55 mmol) and $NaHCO_3$ (84 mg, 1.0 mmol) were added to the reaction mixture. The reaction was conducted

for another 18 hours at ambient temperature. Weinreb amide **2.81i** (88.6 mg, 71%) was obtained as a yellow oil. R_f 0.49 (hexane-EtOAc 1:1)

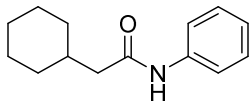
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H), 7.24 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.46 (s, 2H), 3.62 (s, 3H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.14 (s, 3H), 2.43 (t, *J* = 6.6 Hz, 2H), 1.81 – 1.56 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.55, 138.50, 128.29, 127.59, 127.45, 77.27, 72.86, 70.08, 61.15, 31.54, 29.35, 21.41.; IR (neat): : ν_{max} 2962, 2943, 2888, 2862, 2845, 1651, 1419, 1266, 1100, 912, 726 cm^{-1}.; HRMS (ESI) calcd. for $C_{14}H_{21}NO_3Na$ $[M+Na]^+$: 274.14136, found: 274.14142.



5-(benzyloxy)pentanamide (2.81j)

Following the general procedure D using 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol) and ammonium carbamate (59.0 mg, 0.75 mmol, 1.5 equiv), the reaction was heated at 80 °C for 24 hours. **2.81j** (104.4 mg, 98%) was obtained as a yellow powder. R_f 0.09 (hexane-EtOAc 1:1)

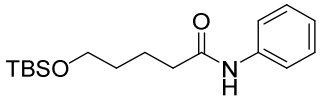
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 5.63 (br s, 2H), 4.47 (s, 2H), 3.49 (t, *J* = 5.9 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.86 – 1.58 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.66, 138.33, 128.38, 127.67, 127.60, 72.99, 70.00, 35.53, 29.01, 22.48.



2-cyclohexyl-*N*-phenylacetamide (2.81k)

Following the general procedure D using ethynylcyclohexane (130.7 μL, 1.0 mmol) and aniline (100 μL, 1.1 mmol), the reaction was heated at 80 °C for 2 hours. **2.81k** (183.0 mg, 84%) was obtained. R_f 0.57 (hexane-EtOAc 5:1)

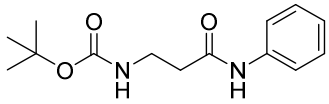
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8 Hz, 2H), 7.35 – 7.11 (m, 3H), 7.03 (t, *J* = 7.3 Hz, 1H), 2.15 (d, *J* = 7.0 Hz, 2H), 1.97 – 1.51 (m, 7H), 1.36 – 1.03 (m, 2H), 1.03 – 0.81 (m, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.00, 138.15, 129.19, 124.40, 120.03, 46.14, 35.73, 33.38, 26.39, 26.27.; HRMS (ESI) calcd. for $C_{14}H_{19}NONa$ $[M+Na]^+$: 240.1359, found: 240.1361.



5-((*tert*-butyldimethylsilyl)oxy)-*N*-phenylpentanamide (2.81l)

Following the general procedure D in 1 mmol scale, using *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (198 mg, 1.0 mmol) and aniline (100 μL, 1.1 mmol), the reaction was heated at 80 °C for 2 hours. **2.81l** (307 mg, 99%) was obtained. R_f 0.71 (hexane-EtOAc, 2:1)

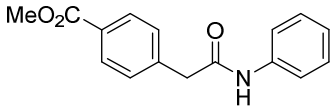
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.03 (t, *J* = 7.3 Hz, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.87 – 1.64 (m, 2H), 1.64 – 1.43 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.29, 138.31, 128.76, 124.09, 120.43, 62.91, 37.14, 32.18, 26.00, 22.37, 18.32, -5.27.; HRMS (ESI) calcd. for $C_{17}H_{29}NO_2SiNa$ $[M+Na]^+$: 330.1860, found: 330.1857.



***tert*-butyl (3-oxo-3-(phenylamino)propyl)carbamate (2.81m)**

Following the general procedure D using *tert*-butyl prop-2-yn-1-ylcarbamate (77.6 mg, 0.5 mmol) and aniline (50 μL, 0.55 mmol), the reaction was heated at 80 ºC for 1 hour. **2.81m** (128.5 mg, 97%) was obtained. R_f 0.23 (hexane-EtOAc, 2:1)

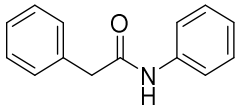
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.30 (dd, *J* = 14.9, 6.9 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.23 (s, 1H), 3.49 (dd, *J* = 12.0, 6.1 Hz, 2H), 2.59 (t, *J* = 5.9 Hz, 2H), 1.43 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.94, 156.60, 138.09, 129.17, 124.53, 120.09, 79.87, 37.80, 36.76, 28.60.; HRMS (ESI) calcd. for $C_{14}H_{20}N_2O_3Na$ $[M+Na]^+$: 287.1366, found: 287.1369.



methyl 4-(2-oxo-2-(phenylamino)ethyl)benzoate (2.81n)

Following the general procedure D with a modification on the stoichiometry, methyl 4-ethynylbenzoate (80.4 μL, 0.5 mmol), aniline (50.1 μL, 0.55 mmol), *N*-hydroxybenzotriazole (270 mg, 2.0 mmol), and $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol) were employed. The reaction was heated at 80 ºC for 5 hours. **2.81n** (120.5 mg, 90%) was obtained as a colorless oil. R_f 0.29 (hexane-EtOAc, 2:1)

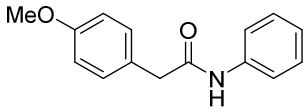
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.35 (m, 5H), 7.35 – 7.21 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.45, 166.95, 139.87, 137.72, 130.47, 129.66, 129.58, 129.17, 124.83, 120.16, 52.39, 44.76.; HRMS (ESI) calcd. for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$: 292.0944, found: 292.0945.



***N*,2-diphenylacetamide (2.81o)**

Following the general procedure D with a modification on the stoichiometry, phenylacetylene (54.9 μL, 0.5 mmol), aniline (50.1 μL, 0.55 mmol), *N*-hydroxybenzotriazole (270 mg, 2.0 mmol), and $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol) were employed. The reaction was heated at 80 °C for 24 hours. Amide **2.81o** (63.1 mg, 60%) was obtained as a colorless oil. R_f 0.43 (hexane-EtOAc 2:1)

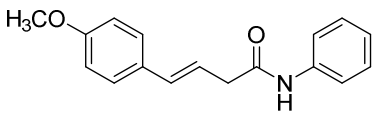
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.22 (m, 9H), 7.15 (s, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.73 (s, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.29, 137.83, 134.65, 129.73, 129.44, 129.14, 127.88, 124.66, 120.03, 45.05.; HRMS (ESI) calcd. for $C_{14}H_{13}NONa$ $[M+Na]^+$: 234.0889, found: 234.0892.



2-(4-methoxyphenyl)-*N*-phenylacetamide (2.81p)

Following the general procedure D with a modification on the stoichiometry, 1-ethynyl-4-methoxybenzene (64.8 μL, 0.5 mmol), aniline (50.1 μL, 0.55 mmol), *N*-hydroxybenzotriazole (270 mg, 2.0 mmol), and $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol) were employed. The reaction was heated at 80 °C for 24 hours. Amide **2.81n** (55.1 mg, 46%) was obtained as a colorless oil. R_f 0.37 (hexane-EtOAc 2:1)

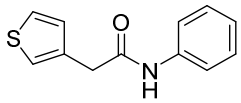
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.21 (m, 4H), 7.08 (t, *J* = 7.3 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.67, 159.36, 137.85, 130.93, 129.15, 126.53, 124.62, 119.95, 114.91, 55.55, 44.21.; HRMS (ESI) calcd. for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$: 264.0995, found: 264.0996.



(*E*)-4-(4-methoxyphenyl)-*N*-phenylbut-3-enamide (2.81q)

Following the general procedure D with a modification on the stoichiometry, (*E*)-1-(but-1-en-3-yn-1-yl)-4-methoxybenzene (79.1 mg, 0.5 mmol), aniline (50.1 μL, 0.55 mmol), *N*-hydroxybenzotriazole (270 mg, 2.0 mmol), and $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol) were employed. The reaction was heated at 80 °C for 12 hours. Amide **2.81q** (85.2 mg, 64%) was obtained as a colorless oil. R_f 0.63 (hexane-EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.14 (dd, *J* = 7.9, 5.3 Hz, 4H), 6.97 (t, *J* = 6.0 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 15.6, 7.2 Hz, 1H), 3.66 (s, 3H), 3.15 (d, *J* = 7.0 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.72, 159.46, 138.00, 134.45, 129.43, 129.02, 127.64, 124.46, 120.19, 119.81, 114.13, 55.36, 41.84.

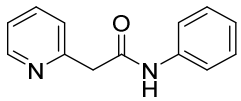


***N*-phenyl-2-(thiophen-3-yl)acetamide (2.81r)**

Following the general procedure D using 3-ethynylthiophene (54 mg, 0.5 mmol) and aniline (50.1 μL, 0.55 mmol), the reaction was heated at 80 °C for 6 hours. Amide **2.81r** (76.7 mg, 72%) was obtained as a yellow solid. R_f 0.26 (hexane-EtOAc 4:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 4.7, 3.0 Hz, 1H), 7.26 (dd, *J* = 12.8, 4.8 Hz, 2H), 7.13 – 7.00 (m, *2*H), 3.73 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.74, 137.57, 134.39, 128.93, 128.43, 127.02,

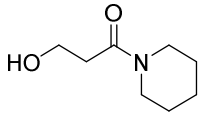
124.47, 123.75, 119.89, 39.09.; HRMS (ESI) calcd. for $C_{12}H_{12}NOS$ $[M+H]^+$: 218.06341, found: 218.06343.



***N*-phenyl-2-(pyridin-2-yl)acetamide (2.81s)**

Following the general procedure D using 2-ethynylpyridine (52 mg, 0.5 mmol, 1.0 equiv), aniline (50.1 μL, 0.55 mmol), and toluene as solvent instead of *t*-BuOH, the reaction was heated at 80 °C for 21 hours. **2.81s** (64.2 mg, 60%) was obtained as a brown gummy oil. R_f 0.15 (hexane-EtOAc 1:1)

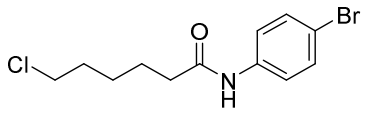
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.58 (d, *J* = 4.3 Hz, 1H), 7.66 (t, *J* = 7.1 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.18 (m, 4H), 7.04 (t, *J* = 7.3 Hz, 1H), 3.85 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.16, 155.38, 148.92, 137.43, 128.55, 128.43, 124.30, 123.96, 122.26, 119.78, 45.81.; HRMS (ESI) calcd. for $C_{13}H_{13}N_2O_1$ $[M+H]^+$: 213.10224, found: 213.10222.



3-hydroxy-1-(piperidin-1-yl)propan-1-one (2.81t)

Following the general procedure D using propargyl alcohol (28 mg, 0.5 mmol, 1.0 equiv) and piperidine (10.9 μL, 0.55 mmol), the reaction was heated at 80 °C for 1 hour. After completion of the reaction, the crude mixture was filtered over silica gel (EtOAc-MeOH 10:1) and purified by column chromatography on silica gel. Amide **2.81t** (67 mg, 85%) was obtained as a yellow oil. R_f 0.35 (EtOAc-MeOH 5:1)

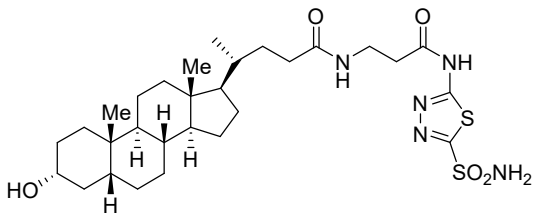
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (t, *J* = 5.0 Hz, 2H), 3.60 (s, 1H), 3.57 – 3.49 (m, 2H), 3.41 – 3.29 (m, 2H), 2.51 (t, *J* = 5.3 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.59 – 1.43 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56, 58.58, 46.28, 42.40, 34.62, 26.22, 25.43, 24.37.; HRMS (ESI) calcd. for $C_8H_{15}NO_2Na$ $[M+Na]^+$: 180.09950, found: 180.09944.



***N*-(4-bromophenyl)-6-chlorohexanamide (2.81u)**

Following the general procedure D using 6-chloro-1-hexyne (58 mg, 0.5 mmol, 1.0 equiv) and 4-bromoaniline (94.6 mg, 0.55 mmol), the reaction was heated at 80 °C for 1 hour. **2.81u** (138 mg, 90%) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.37 (q, *J* = 8.9 Hz, 4H), 3.48 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.83 – 1.55 (m, 4H), 1.52 – 1.30 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.91, 137.13, 131.89, 121.96, 116.96, 44.93, 37.26, 32.28, 26.50, 24.86.; HRMS (ESI) calcd. for $C_{12}H_{16}BrClNO$ $[M+H]^+$: 304.00983, found: 304.00986.

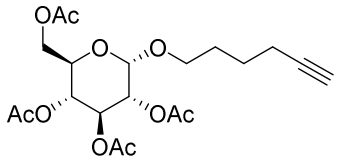


Experimental Procedure and Partial Characterization of

(*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-*N*-(3-oxo-3-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)propyl)pentanamide (2.81v)

Following the general procedure D, the reaction was heated at 80 °C for 18 hours. **2.81v** (86.3 mg, 71%) was obtained as a white solid. R_f 0.40 (DCM-MeOH 6:1)

^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) δ 3.64 – 3.44 (m, 4H), 3.31 (s, 1H), 2.73 (t, *J* = 6.1 Hz, 2H), 2.26 – 2.13 (m, 1H), 2.12 – 1.98 (m, 1H), 1.98 – 1.88 (m, 1H), 1.88 – 1.66 (m, 5H), 1.56 (m, 2H), 1.49 – 0.95 (m, 21H), 0.91 (m, *J* = 16.9 Hz, 6H), 0.62 (s, 3H).; HRMS (ESI) calcd for $C_{29}H_{48}N_5O_5S_2$ $[M+H]^+$: 610.30914, found: 610.30914.

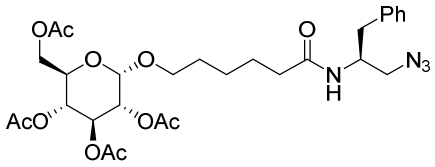


(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(hex-5-yn-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (S2.5)

To a solution of *β*-D-glucopyranose pentaacetate (1 g, 2.56 mmol)[29] and 5-hexyn-1-ol (342 *μl*, 3.07 mmol) in DCM (3 ml) was added BF_3 etherate (629 *μl*, 5.1 mmol) dropwise at 0 °C. After stirring for 2 days at rt, the mixture was diluted with DCM (10 ml), washed with saturated $NaHCO_3$ solution (3 times) and brine (1 time), dried over Na_2SO_4 and concentrated. Purification with column chromatography on SiO_2 afforded **S2.5** (200 mg) as a colorless liquid. R_f 0.34 (hexane:EtOAc 2:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (t, *J* = 9.5 Hz, 1H), 5.08 (t, *J* = 9.7 Hz, 1H), 4.99 (dd, *J* = 9.5, 8.1 Hz, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.26 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.14 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.90 (dt, *J* = 9.8, 6.0 Hz, 1H), 3.69 (ddd, *J* = 9.9, 4.6, 2.4 Hz, 1H), 3.58 – 3.44 (m, 1H), 2.20 (td, *J* = 7.0, 2.6 Hz, 2H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.62 – 1.53 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ

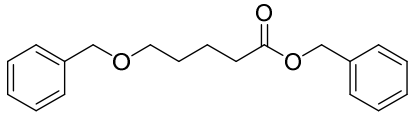
170.58, 170.20, 169.32, 169.21, 100.70, 83.98, 76.72, 72.75, 71.68, 71.22, 69.33, 68.56, 68.37, 61.89, 28.27, 24.71, 20.68, 20.59, 20.55, 17.92.



(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((6-(((*S*)-1-azido-3-phenylpropan-2-yl)amino)-6-oxohexyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2.81w)

Following the general procedure D using (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(hex-5-yn-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**S2.5**) (214.2 mg, 1 mmol) and (*S*)-1-azido-3-phenylpropan-2-amine (96.8 mg, 1.1 mmol), the reaction was heated at 80 ºC for 3.5 h. Amide **2.81w** (269.5 mg, 87%) was obtained. R_f 0.14 (hexane-EtOAc 1:1)

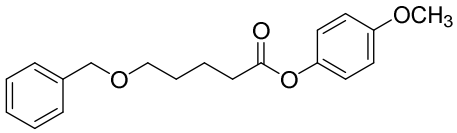
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 5H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.21 (t, *J* = 9.5 Hz, 1H), 5.09 (t, *J* = 9.6 Hz, 1H), 4.98 (t, *J* = 8.7 Hz, 1H), 4.48 (d, *J* = 7.9 Hz, 1H), 4.39 – 4.21 (m, 2H), 4.15 (d, *J* = 12.1 Hz, 1H), 3.90 – 3.77 (m, 1H), 3.69 (d, *J* = 8.1 Hz, 1H), 3.47 (d, *J* = 8.5 Hz, 2H), 3.33 (dd, *J* = 12.3, 3.7 Hz, 1H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.22 – 1.91 (m, 14H), 1.66 – 1.46 (m, 4H), 1.29 (dd, *J* = 14.7, 7.5 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.54, 170.62, 170.18, 169.34, 169.31, 136.97, 129.10, 128.61, 126.74, 100.75, 77.26, 72.71, 71.65, 71.25, 69.87, 68.37, 61.86, 52.97, 49.80, 37.68, 36.41, 28.94, 25.39, 25.09, 20.68, 20.62, 20.55.; HRMS (ESI) calcd. for $C_{29}H_{40}N_4O_{11}Na$ $[M+Na]^+$: 643.25858, found: 643.25824.



benzyl 5-(benzyloxy)pentanoate (2.82a)

Following the general procedure E using benzyl alcohol (57 μL, 0.55 mmol), the reaction was heated at 80 °C for 20 hours. **2.82a** (136 mg, 91%) was obtained. R_f 0.63 (hexane-EtOAc 1:1)

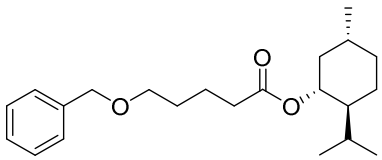
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 10H), 5.11 (s, 2H), 4.48 (s, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.80 – 1.70 (m, 2H), 1.70 – 1.58 (m, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.55, 138.71, 136.27, 128.72, 128.54, 128.35, 127.78, 127.70, 73.06, 69.95, 66.29, 34.19, 29.31, 21.94.; HRMS (ESI) calcd. for $C_{19}H_{22}O_3Na$ $[M+Na]^+$: 321.14612, found: 321.14618.



4-methoxyphenyl 5-(benzyloxy)pentanoate (2.82b)

Following the general procedure E using 4-methoxyphenol (68 mg, 0.55 mmol), the reaction was heated at 80 °C for 21 hours. Ester **2.82b** (129.6 mg, 82%) was obtained. R_f 0.46 (hexane-EtOAc 1:1)

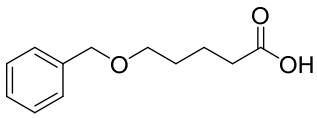
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.73 (dt, *J* = 12.9, 6.2 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.55, 157.32, 144.36, 138.66, 128.53, 127.77, 127.70, 122.45, 114.56, 73.07, 69.91, 55.71, 34.17, 29.28, 21.97.; HRMS (ESI) calcd. for $C_{19}H_{22}O_4Na$ $[M+Na]^+$: 337.14103, found: 337.14102.



(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 5-(benzyloxy)pentanoate (2.82c)

Following the general procedure E using (1*R*,2*S*,5*R*)-(-)-menthol (86.0 mg, 0.55 mmol), the reaction was heated at 80 °C for 66 hours. Ester **2.82c** (115.5 mg, 67%) was obtained. R_f 0.69 (hexane-EtOAc 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 5H), 4.68 (td, *J* = 10.9, 4.4 Hz, 1H), 4.49 (s, 2H), 3.48 (t, *J* = 6.1 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.93 (m, 1H), 1.85 (ddd, *J* = 14.0, 7.0, 2.7 Hz, 1H), 1.78 – 1.58 (m, 6H), 1.54 – 1.41 (m, 1H), 1.36 (ddd, *J* = 14.1, 6.1, 3.1 Hz, 1H), 1.12 – 0.79 (m, 9H), 0.76 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.26, 138.70, 128.49, 127.73, 127.65, 74.09, 73.01, 69.95, 47.16, 41.11, 34.56, 34.43, 31.52, 29.31, 26.41, 23.57, 22.19, 22.04, 20.92, 16.46.; HRMS (ESI) calcd. for $C_{22}H_{34}O_3Na$ $[M+Na]^+$: 369.24002, found: 369.23990.

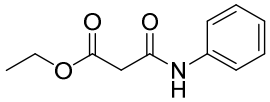


5-(benzyloxy)pentanoic acid (2.82d)[31]

To a solution of 5-(benzyloxy)-pent-1-yne (87.1 mg, 0.5 mmol), *N*-hydroxybenzotriazole (74.3 mg, 0.55 mmol), and $CpRu(PPh_3)_2Cl$ (36.3 mg, 0.05 mmol) in *t*-BuOH (1.25 mL, 0,4 M) was added 5% $NaHCO_{3(aq)}$ (0.25 mL) After bubbling with argon gas for approximately 30 seconds, the reaction was heated at 80 °C for 18 h. In this case, 3 N HCl solution was used for washing instead of saturated $K_2CO_{3(aq)}$ solution. Flash column chromatography on SiO_2 (DCM-MeOH 97:3) afforded **2.82d** (84.4 mg, 81%) as a yellow oil, which was very closely placed to triphenylphosphine oxide byproduct on SiO_2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 4.50 (s, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.37 (t, *J* = 7.1 Hz, 2H), 1.81 – 1.60 (m, 4H).; ^{13}C NMR (100 MHz,

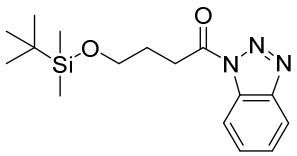
$CDCl_3$) δ 179.70, 138.34, 128.36, 127.64, 127.56, 72.89, 69.71, 33.74, 28.99, 21.48.



ethyl 3-oxo-3-(phenylamino)propanoate (2.87)

With a modification to the general procedure D, ethyl propiolate (49 mg, 0.5 mmol) and toluene (1.25 mL) were employed as an alkyne and solvent respectively. The reaction was heated at 80 °C for 1 h and cooled down to ambient temperature. After addition of aniline (50.1 μL, 0.55 mmol), the reaction was stirred at rt for another 1 h. Malonamide **2.87** (82 mg, 79%) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.45 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.66, 163.22, 137.47, 128.92, 124.53, 120.11, 61.84, 41.78, 14.01.; HRMS (ESI) calcd. for $C_{11}H_{13}N_1O_3Na$ $[M+Na]^+$: 230.07876, found: 230.07875.

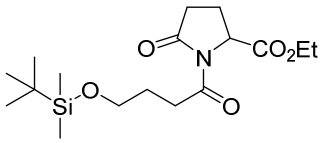


1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)butan-1-one (2.89)

With a modification to the general procedure D, 4-((*tert*-butyldimethylsilyl)oxy)-1-butyne (1.8435g, 10 mmol), HOBt (1.4863 g, 11 mmol), $CpRu(PPh_3)_2Cl$ (145.3 mg, 0.2 mmol, 2 mol%) and toluene (25 mL) were employed. The reaction was heated at 80 °C for 21 hours. Acyl-

benzotriazole **2.89** (2.8905 g, 90%) was obtained as a yellow oil. R_f 0.38 (Hexane-EtOAc 19:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 3,45 (t, *J* = 8.4 Hz, 2H), 2.12 – 2.02 (m, 2H), 0.78 (s, 9H), -0.05 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.44, 146.05, 131.01, 130.10, 125.87, 119.96, 114.34, 61.83, 32.15, 27.41, 25.78, 18.16, -5.51.



ethyl 1-(4-((*tert*-butyldimethylsilyl)oxy)butanoyl)-5-oxopyrrolidine-2-carboxylate (2.93)

In a 5 mL vial equipped with a screw cap, a solution of 4-((*tert*-butyldimethylsilyl)oxy)-but-1-yne (91.2 mg, 0.5 mmol),[30] *N*-hydroxybenzotriazole (149.0 mg, 1.1 mmol), and $CpRu(PPh_3)_2Cl$ (18.1 mg, 0.025 mmol), DMAP (6.1 mg, 0.05 mmol) in *t*-BuOH (1.25 mL, 0.4 M) was thoroughly bubbled with argon gas for approximately 30 seconds, before the vial was tightly sealed. The reaction was heated at 70 °C for 1h and cooled down to ambient temperature. Ethyl 2-aminopent-4-ynoate (78.0 mg, 0.55 mmol) was added and the solution was again bubbled with argon gas, before capped and sealed. The reaction was leaved to stir at ambient temperature for 2 h, and another 6 h at 80 °C. The mixture was poured into EtOAc and washed with saturated $K_2CO_{3(aq)}$ solution three times and brine. Followed after drying ($MgSO_4$) and evaporation was flash column chromatography on SiO_2 affording **2.93** (109.9 mg, 61%). R_f 0.21 (hexane-EtOAc 4:1)

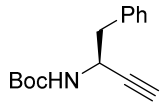
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (dd, *J* = 9.4, 2.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.76 – 2.61 (m, 1H), 2.52 (ddd, *J* = 17.6, 9.3, 3.1 Hz, 1H), 2.35 – 2.24 (m, 2H), 2.09 – 2.00 (m, 1H), 1.88 – 1.78 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.26, 173.94, 171.07, 62.08, 61.63, 57.94, 33.18, 31.95, 27.04, 25.89, 21.36, 18.27, 14.04, -5.39.

General Procedure F: Synthesis of Dipeptides from Boc-Protected Propargylamines

A mixture of a terminal alkyne (1 equiv), 1-hydroxybenzotriazole (1 equiv), $CpRu(PPh_3)_2Cl$ (5 mol%), DMAP (10 mol%) in toluene (0.5 ml) was stirred at 80 °C until the alkyne disappeared on TLC. After the mixture was cooled down to ambient temperature, a propargylic amine-HCl salt (1 equiv), TEA (3 equiv) and *t*-BuOH (0.5 ml) were added and stirred for 12 h at 80 °C. The reaction mixture was diluted with DCM (3 ml) and washed with 1N NaOH (3 ml, 3 times). After filtration through silica gel, and concentration, the crude product was purified by flash column chromatography on silica gel to afford a dipeptide.

General Procedure G: Elongation of Amino Alkynes for Tripeptide Synthesis

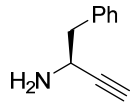
A mixture of a terminal alkyne (0.01 mmol), 1-hydroxybenzotriazole (0.01 mmol), $CpRu(PPh_3)_2Cl$ (0.001 mmol), and DMAP (0.002 mmol) in *t*-BuOH (0.1 ml) was heated to 80 °C in a screw cap vial and stirred for 2 h. After cooling to room temperature, a propargylic amine-HCl salt (0.01 mmol), TEA (0.03 mmol) and *t*-BuOH (0.2 ml) were added and stirred for 12 h at 80 °C. The reaction mixture was diluted with DCM (3 ml) and washed with 1N NaOH (3 ml, 3 times). After filtration on silica gel, and concentration, the crude product was purified by Prep-HPLC to afford a peptide.



***tert*-butyl (*S*)-(1-phenylbut-3-yn-2-yl)carbamate (S2.6)**

To a flame-dried round bottom flask equipped with magnetic stir bar containing , *tert*-butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (1.2335 g, 4.0 mmol), and THF (40 ml) was added LAH solution (3.0 ml, 2 M in THF, 6.0 mmol) dropwise at 0 °C. The mixture was stirred at this temperature for 30 min before quenched with 10% $KHSO_{4(aq)}$ solution (30 ml) (caution: exothermic) and phases were separated. The aqueous layer was extracted with Et_2O (40 ml, three times), and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (50 ml) and brine (50 ml), dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was re-dissolved in MeOH (8.0 ml) and cooled down with ice-water bath. dimethyl (1-diazo-2-oxopropyl)phosphonate (1.3561 g, 85% wt. in toluene, 6.0 mmol) was added to the mixture and anhydrous K_2CO_3 (829.3 mg, 6.0 mmol) was added in one portion (Note: excess potassium carbonate can cause epimerization). The reaction was stirred at 0 °C for 1 hour and another 15 hours at ambient temperature. The mixture was diluted with Et_2O (30 ml) and poured into water (30 ml). The organic phases were further washed with water (30 ml) and brine (30 ml), dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel to yield **S2.6** (804.5 mg, 82% for 2 steps) as a yellow oil. R_f 0.57 (hexane-EtOAc 6:1)

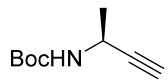
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 5H), 4.79 (br s, 1H), 4.67 (br s, 1H), 2.96 (qd, *J* = 13.3, 6.3 Hz, 2H), 2.26 (d, *J* = 1.7 Hz, 1H), 1.42 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.56, 136.34, 129.76, 128.26, 126.86, 82.79, 77.39, 77.28, 77.07, 76.75, 72.17, 43.84, 41.72, 31.56, 28.31.; HRMS mass calcd. for $C_{15}H_{19}NO_2Na$ $[M+Na]^+$: 268.1308, found 268.1309.



(*S*)-1-phenylbut-3-yn-2-amine (S2.7)

To a solution of *tert*-butyl (*S*)-(1-phenylbut-3-yn-2-yl)carbamate (720.1 mg, 3.0 mmol) in anhydrous DCM (6 ml) was added TFA (6 ml) slowly at 0 °C. After stirring at rt for 30 min, the mixture was evaporated and excess TFA was further removed by azeotropic evaporation with toluene (10 ml × 3). The mixture was diluted with DCM (10 ml) and neutralized with saturated $NaHCO_3$ solution. The aqueous phase was extracted with DCM (10 ml × 3), and combined organic extract were dried(Na_2SO_4), filtered, and evaporated affording (**S2.7**) (397.5 mg, 91%) as a colorless oil which was pure enough to conduct next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H), 3.87 – 3.76 (m, 1H), 2.96 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.87 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.34 – 2.28 (m, 1H), 1.44 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.36, 129.58, 128.34, 126.75, 86.90, 77.47, 77.15, 76.83, 71.28, 44.62, 44.13.

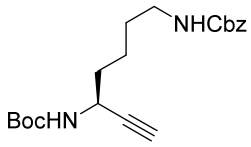


***tert*-butyl (S)-but-3-yn-2-ylcarbamate (S2.8)**

tert-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (390.2 mg, 1.68 mmol) afforded *tert*-butyl (*S*)-but-3-yn-2-ylcarbamate as a white solid (170.7 mg, 60% for 2 steps) by analogous procedure for preparation of **S2-7**. R_f 0.63 (hexane-EtOAc 6:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (br s, 1H), 4.20 (br s, 1H), 1.97 (d, *J* = 1.8 Hz, 1H), 1.17 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ

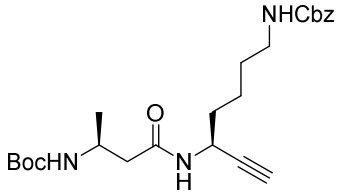
154.56, 84.51, 77.30, 76.98, 76.66, 70.07, 38.20, 28.31, 22.51.; HRMS mass calcd. for $C_9H_{15}NO_2Na$ $[M+Na]^+$, 192.0995, found 192.0996.



benzyl *tert*-butyl hept-6-yne-1,5-diyl(*S*)-dicarbamate (S2.9)

Benzyl *tert*-butyl (6-(methoxy(methyl)amino)-6-oxohexane-1,5-diyl)(*S*)-dicarbamate (423.5 mg, 1.0 mmol) gave benzyl *tert*-butyl hept-6-yne-1,5-diyl(*S*)-dicarbamate as an yellow oil (337.9 mg, 94% for 2 steps) by analogous procedure for preparation of **S2.7**. R_f 0.58 (hexane-EtOAc 3:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 5H), 5.07 (s, 2H), 4.76 (br s, 1H), 4.69 (br s, 1H), 4.37 (br s, 1H), 3.25 – 3.08 (m, 2H), 2.24 (d, *J* = 2.1 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.60 – 1.48 (m, 4H), 1.42 (s, 9H).; HRMS mass calcd. for $C_{20}H_{28}N_2O_4Na$ $[M+Na]^+$ 383.1941, found 383.1940.

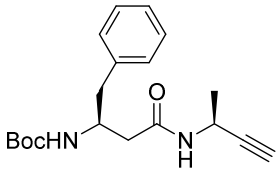


***tert*-butyl ((*S*)-4-(((*S*)-7-(((benzyloxy)carbonyl)amino)hept-1-yn-3-yl)amino)-4-oxobutan-2-yl)carbamate (S2.10)**

Following the general procedure F using *tert*-butyl (*S*)-but-3-yn-2-ylcarbamate (16.9 mg, 0.1 mmol), **S2.10** (33.3 mg, 75%) was obtained. R_f 0.42 (hexanes-EtOAc 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.28 (s, 1H), 5.14 (s, 1H), 5.09 (s, 2H), 4.95 (s, 1H), 4.71 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.02 – 3.86 (m, 1H),

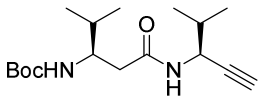
3.28 – 3.04 (m, 2H), 2.37 (d, *J* = 5.6 Hz, 2H), 2.25 (d, *J* = 1.9 Hz, 1H), 1.67 (s, 2H), 1.60 – 1.49 (m, 2H), 1.48 – 1.35 (m, 11H), 1.20 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13, 156.71, 155.67, 136.79, 128.72, 128.29, 128.28, 83.11, 79.61, 71.46, 66.80, 44.38, 42.89, 41.09, 40.83, 35.18, 29.46, 28.63, 22.74, 20.92.; HRMS (ESI) calcd. for $C_{24}H_{35}N_3O_5Na$ [M+Na]+: 468.24689, found: 468.24668.



***tert*-butyl ((*S*)-4-(((*S*)-but-3-yn-2-yl)amino)-4-oxo-1-phenylbutan-2-yl)carbamate (S2.11)**

Following the general procedure F using *tert*-butyl (*S*)-(1-phenylbut-3-yn-2-yl)carbamate (23.1 mg, 0.1 mmol) and *tert*-butyl (*S*)-but-3-yn-2-ylcarbamate (16.1 mg, 0.1 mmol), **S2.11** (27.4 mg, 83%) was obtained.

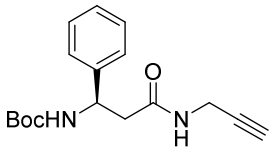
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 5H), 5.89 (s, 1H), 5.36 (s, 1H), 4.89 – 4.71 (m, 1H), 4.09 (dd, *J* = 11.4, 6.4 Hz, 1H), 2.99 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.79 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.42 (dd, *J* = 15.1, 4.6 Hz, 1H), 2.35 – 2.15 (m, 2H), 1.41 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.84, 155.64, 138.03, 129.37, 128.64, 126.65, 83.96, 77.48, 77.06, 76.64, 70.49, 49.52, 40.53, 39.24, 36.80, 28.42, 22.05.; HRMS (ESI) calcd. for $C_{19}H_{26}N_2O_3Na$ [M+Na]+: 353.18356, found: 353.18356.



***tert*-butyl ((*R*)-4-methyl-1-(((*S*)-4-methylpent-1-yn-3-yl)amino)-1-oxopentan-3-yl)carbamate (S2.12)**

Following the general procedure F using *tert*-butyl (*S*)-(4-methylpent-1-yn-3-yl)carbamate (19.7 mg, 0.1 mmol), **S2.12** (19.6 mg, 63%) was obtained.

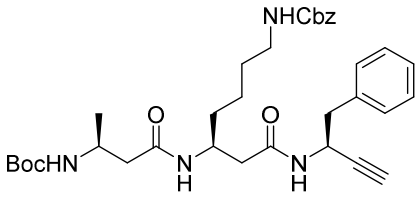
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 4.97 (s, 1H), 4.64 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.66 (s, 1H), 2.52 – 2.33 (m, 2H), 2.24 (dd, *J* = 3.1, 1.2 Hz, 1H), 2.00-1.75 (m, 2H), 1.43 (s, 9H), 1.08 – 0.95 (m, 6H), 0.95 – 0.80 (m, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.14, 156.10, 81.67, 71.81, 53.48, 47.13, 39.50, 32.49, 28.43, 19.43, 18.92, 18.39, 17.67.; HRMS (ESI) calcd. for $C_{17}H_{30}N_2O_3Na$ $[M+Na]^+$: 333.21486, found: 333.21481.



***tert*-butyl (*R*)-(3-oxo-1-phenyl-3-(prop-2-yn-1-ylamino)propyl)carbamate (S2.13)**

Following the general procedure F using *tert*-butyl (*R*)-(1-phenylprop-2-yn-1-yl)carbamate and propargylamine, **S2.13** (23 mg, 75%) was obtained.

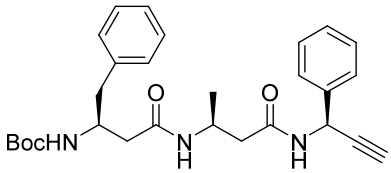
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.12 (m, 5H), 5.91 (s, 2H), 5.00 (s, 1H), 4.02 – 3.80 (m, 2H), 2.69 (d, *J* = 14.1 Hz, 2H), 2.16 (t, *J* = 2.4 Hz, 1H), 1.39 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.01, 155.50, 141.40, 128.74, 127.53, 126.07, 79.84, 79.12, 71.66, 51.85, 42.72, 29.17, 28.40.; HRMS (ESI) calcd. for $C_{17}H_{22}N_2O_3Na$ $[M+Na]^+$: 325.15226, found: 325.15228.



***tert*-butyl ((*S*)-4-(((*S*)-7-(((benzyloxy)carbonyl)amino)-1-oxo-1-(((*S*)-1-phenylbut-3-yn-2-yl)amino)heptan-3-yl)amino)-4-oxobutan-2-yl)carbamate (2.94)**

Following the general procedure G using **S2.10** (4.5 mg, 0.01 mmol) and **S2.7** (1.5 mg, 0.01 mmol), **2.94** (3.0 mg, 49%) was obtained.

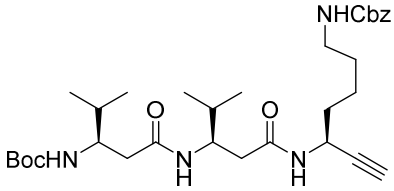
HPLC-Mass (ESI): MeCN:H_2O=50:50, RT 17.0 min., m/z 629.5 [M+Na], 607.5 [M+H], 507.45 [M+H-Boc]; HRMS (ESI) calcd. for $C_{34}H_{47}N_4O_6$ [M+H]+: 607.34901, found: 607.34900.



***tert*-butyl ((*S*)-4-oxo-4-(((*S*)-4-oxo-4-(((*R*)-1-phenylprop-2-yn-1-yl)amino)butan-2-yl)amino)-1-phenylbutan-2-yl)carbamate (2.95)**

Following the general procedure G using **S2.11** (0.03 mmol) and (*R*)-1-phenylprop-2-yn-1-amine·TFA (0.03 mmol), **2.95** (9.8 mg, 67%) was obtained.

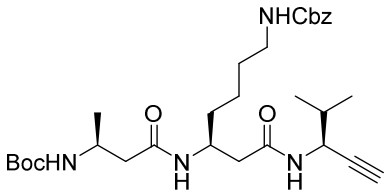
HPLC-Mass (ESI): MeCN:H_2O=50:50, RT 11.5 min., m/z 478.3 [M+H]; HRMS (ESI) calcd. for $C_{28}H_{35}N_3O_4Na$ [M+Na]+: 500.25198, found: 500.25189.



***tert*-butyl ((9*S*,13*R*,17*R*)-9-ethynyl-13-isopropyl-18-methyl-3,11,15-trioxo-1-phenyl-2-oxa-4,10,14-triazanonadecan-17-yl)carbamate (2.96)**

Following the general procedure G using **S2.12** (9.3 mg, 0.03 mmol) and benzyl (*S*)-(5-aminohept-6-yn-1-yl)carbamate (7.8 mg, 0.03 mmol), **2.96** (14.2 mg, 78%) was obtained.

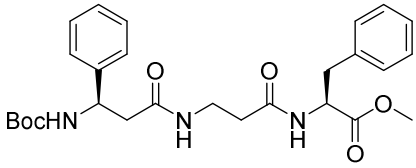
HPLC-Mass (ESI): MeCN:H_2O=50:50, RT 18.5 min., m/z 587.6 [M+H], 487.5 [M+H-Boc], 609.5 [M+Na]; HRMS (ESI) calc'd for $C_{32}H_{50}N_4O_6Na$ [M+Na]+: 609.36226, found: 609.36230.



***tert*-butyl ((*S*)-4-(((*S*)-7-(((benzyloxy)carbonyl)amino)-1-(((*S*)-4-methylpent-1-yn-3-yl)amino)-1-oxoheptan-3-yl)amino)-4-oxobutan-2-yl)carbamate (2.97)**

Following the general procedure G using **S2.10** (16.7 mg, 0.0374 mmol) and (*S*)-4-methylpent-1-yn-3-amine·HCl (5.6 mg, 0.037 mmol), **2.97** (14 mg, 68%) was obtained.

HPLC-Mass (ESI): MeCN:H_2O=50:50, RT 17 min., m/z 559.3 [M+H]; HRMS (ESI) calc'd for $C_{30}H_{46}N_4O_6Na$ $[M+Na]^+$: 581.33095, found: 581.33087.



methyl (3-((*R*)-3-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)propanoyl)-L-phenylalaninate (2.98)

Following the general procedure G using **S2.13** (9.1 mg, 0.03 mmol) and H-(*S*)-Phe-OMe·HCl (6.5 mg, 0.03 mmol), **2.98** (7.8 mg, 52%) was obtained.

HPLC-Mass (ESI): MeCN:H_2O=50:50, RT 8.0 min., m/z 520.35 [M+Na], 498.3 [M+H]; HRMS (ESI) calcd. for $C_{27}H_{35}N_3O_6Na$ $[M+Na]^+$: 520.24181, found: 520.24170.

2.4.3. References

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Chapter 3. Studies toward Total Synthesis of (+)-Fendleridine

3.1. Introduction

3.1.1. Isolation and Structure

(+)-Fendleridine was isolated from the seeds of the Venezuelan tree *Aspidosperma fendleri* WOODSON in 1964 by the Burnell group,[1] and was also found in *Aspidosperma rhombeosignatum* MARKGRAF.[2] Burnell and Medina proposed its structure as hexacyclic indoline **3.1** representing the simplest structure among the bases extracted from *Aspidosperma fendleri* (Figure 3.1).

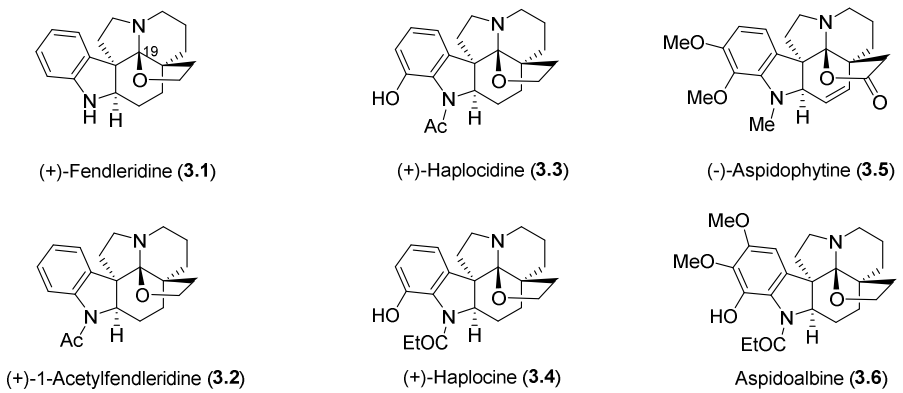


Figure 3.1. (+)-Fendleridine and Related Natural Products

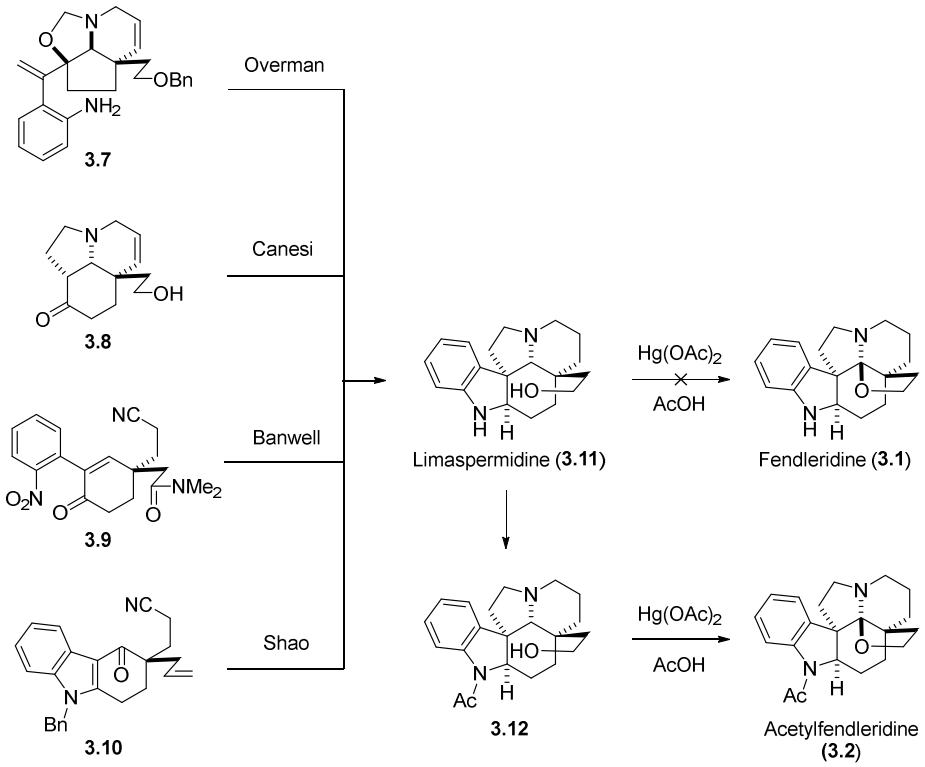
Another member of this family, 1-acetylaspidoalbidine (**3.2**) was also isolated from a botanic source, *Vallesia dichotoma* RUIZ *et* PAV, in 1963 by Djerassi and coworkers.[3,4] While both natural products do not have any noticeable biological activity, they have received much attention from the synthetic community nonetheless, as they represent an archetypal structure encompassing a diverse range of the aspidoalbine natural products. For example, the potent capase-8 inhibitor (+)-haplocidine (**3.3**) and its congener haplocine (**3.4**) have nearly identical structure as acetylaspidoalbidine, differing only in the oxidation state of the aromatic ring.[5]

While Djerassi and coworkers reported that acidic hydrolysis of acetylfendleridine (**3.2**) gave rise to fendleridine (**3.1**),[3] Ban and coworkers invoked the infeasibility of such manipulation in their first total synthesis of (±)–fendleridine.[6] However, an inverse process is facile. The Boger and the Movassaghi groups successfully conducted *N*–acetylation of fendleridine, accessing acetylfendleridine.[7,8] On the basis of these findings regarding with interconversion of the two natural products, a synthesis of fendleridine is deemed more desirable than that of acetylfendleridine.

3.1.2. Reported Syntheses

Structurally, fendleridine possesses four contiguous stereogenic centers all lying on the central cyclohexane ring, among which two of them are quaternary centers. Characteristics in the molecular structure also include an *N,O*–ketal moiety on the C19 position, whose oxidation state is higher than that of

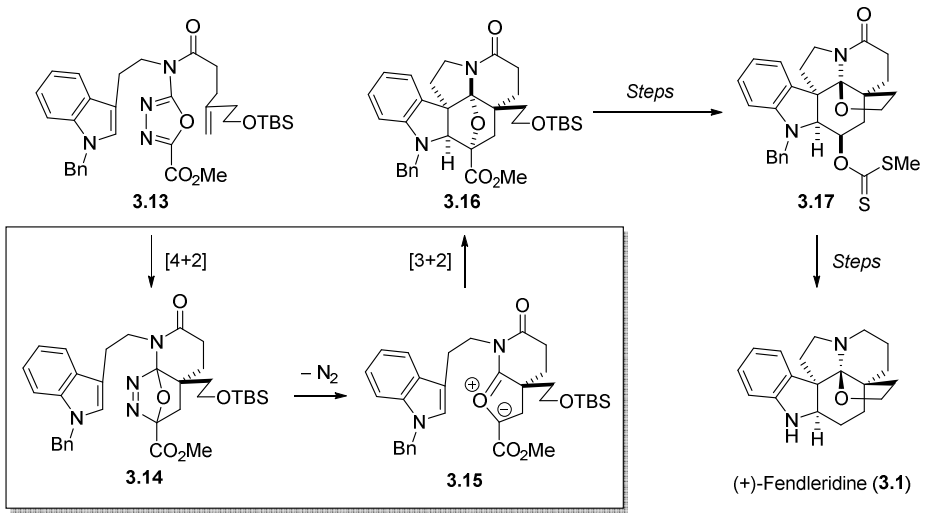
aspidospermidine family. It is this oxidation state where most of the reported syntheses[6,8-14] planned to deal with at the late stage of synthesis.



Scheme 3.1. Formal Syntheses of Acetylfendleridine

However, oxidative conditions developed by the Ban group were claimed to be irreproducible. As a result, the legitimacy of formal syntheses of fendleridine has been unsettled to date, while acetylfendleridine has been synthesized formally by the groups of Overman,[9] Canesi,[10] Banwell,[11] and Shao[12] (Scheme 3.1). In addition to Ban's oxidation conditions, acetylfendleridine (**3.2**) was prepared 21% yield from **3.12** by treatment with iodine, presumably via a

hydroxyl radical intermediate. However, when the same conditions were applied to limaspermidine (**3.11**), no sign of formation of fendleridine (**3.1**) was detected, implying that the unprotected indoline had a deleterious effect on oxidation.[13]

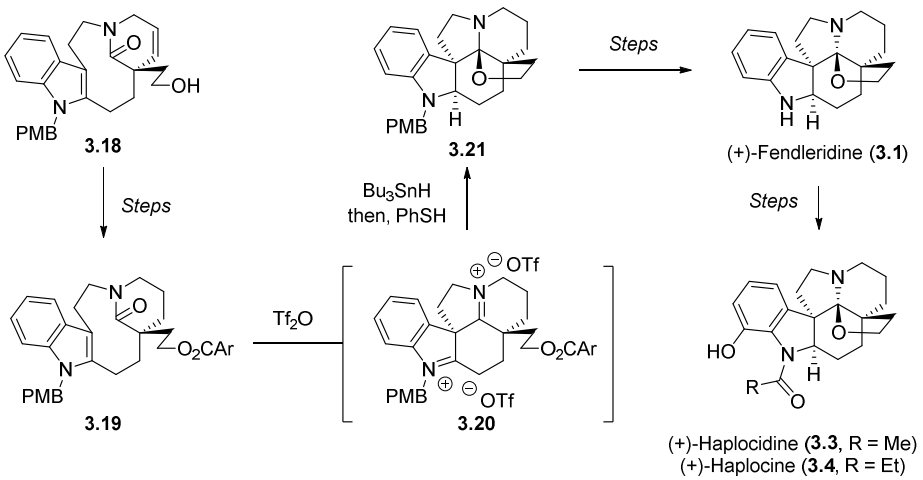


Scheme 3.2. Boger's Total Synthesis of (+)–Fendleridine

In 2010, Boger and coworkers reported a landmark synthesis of (+)-fendleridine using their signature cascade reaction, which consisted of [4 + 2] cycloaddition, dinitrogen extrusion, and [3 + 2] cycloaddition from oxadiazole **3.13** (Scheme 3.2).[7] Noteworthy is the rapid construction of the pentacyclic core of **3.16**, starting from a tryptamine derivative. Although the synthetic route was chemically racemic, enantiomers were separable by chiral HPLC at the

stage of xanthate ester **3.17**, confirming the absolute stereochemistry of fendleridine for the first time, as to have a positive optical rotation.

More recently, White and Movassaghi finished their way to the synthesis of (+)-fendleridine, along with demonstration of a late-stage functionalization approach to fendleridine, affording haplocine and haplocidine.[8] In this case, an optically active compound was separated by enzymatic resolution at the stage of carbinol **3.18**, which eventually went through a series of transannular ring-closure, reduction, and *N*,*O*–ketal formation en route toward (+)–fendleridine (Scheme 3.3).



Scheme 3.3. Movassaghi's Synthesis of (+)-Fendleridine

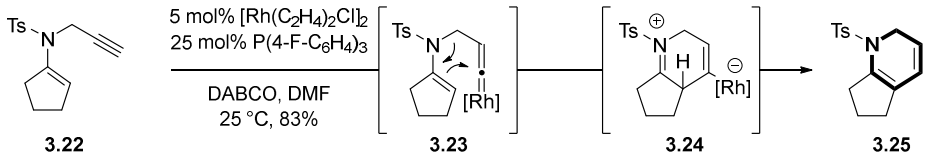
The Boger's work featured total synthesis of an indole monoterpenoid from tryptamine, rapid construction of the core through cascade cycloaddition, and early establishment of the oxidation state on C19. The Movassaghi synthesis is

notable in the perspective of redox-strategy, as their synthesis constitutes the only example where the oxidation state on C19 is reduced during synthesis, not oxidized. On the basis of these precedent synthetic works, we devised our own synthesis toward (+)–fendleridine that would address remaining challenges.

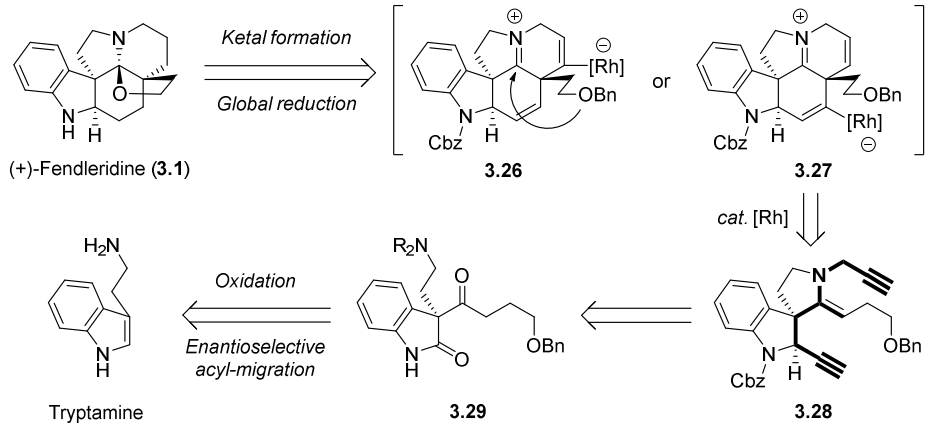
3.2. Synthetic Studies toward (+)-Fendleridine

3.2.1. Retrosynthetic Analysis

Our retrosynthesis is contrived from a notion that the two six-membered rings can be made using metal vinylidene-mediated catalysis. In particular, our group reported cycloisomerization of *N*–propargylenamines to produce six-membered azacycle **3.25**, which can be utilized in the synthesis of fendleridine (Scheme 3.4).[15]



Scheme 3.4. Cycloisomerization of *N*-propargylenamine



Scheme 3.5. Retrosynthetic Analysis for (+)–Fendleridine

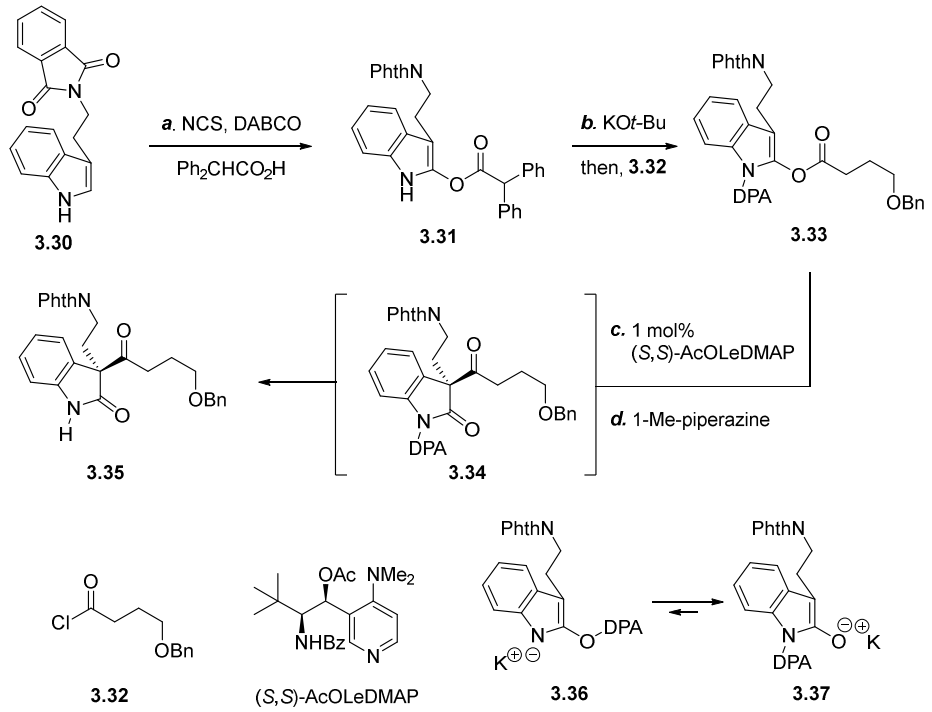
Using this reaction as a key cyclization event, diyne **3.28** is expected to undergo two sequential cycloisomerization to afford pentacyclic intermediate **3.26** or **3.27** (Scheme 3.5). In the absence of an acidic α-proton on iminium intermediate, the ethereal oxygen may quench the iminium ion to form the final tetrahydrofuran ring, from which global reduction will lead to fendleridine (**3.1**). To access the advanced intermediate **3.28**, oxidation of tryptamine and acyl-migration from the resultant oxindole were considered, which would give rise to enantiopure ketone **3.29**. A sequence of reduction of the oxindole, alkynylation, and condensation reaction is envisaged to furnish the key diyne compound **3.28**.

Our retrosynthetic plan aims to synthesize (+)–fendleridine enantioselectively, using metal-vinylidene-mediated cascade cyclization, and starting from tryptamine. This synthesis will demonstrate that transition metal catalysis of

terminal alkynes can serve as powerful means to construct an exquisite molecular architecture even in a complex setting.

3.2.2. Enantioselective Synthesis of 3-Acyloxindole

Our synthesis commenced with oxidation of indole **3.30** (Scheme 3.6). Upon treatment with *N*–chlorosuccinimide, indole **3.30** was transiently chlorinated at indole 3-position, and addition of diphenylacetic acid in the presence of an amine base resulted in 2-oxycarbonylated indole **3.31**. Deprotonation of the indole N–H proton of **3.31** induced *O*-to-*N* migration of a diphenylacetyl (DPA) group, forming less basic anion **3.37**. Subsequent addition of acid chloride **3.32** furnished the *O*–acylated *N*-DPA-oxindole **3.33** in excellent yield. In the absence of the 18-crown-6, *C*–acylation of oxindole enolate **3.37** intervened to produce racemic **3.34** up to 10% yield. The chiral DMAP catalyst developed by Vedejs and coworkers was applied at this stage, generating the first quaternary center at the oxindole 3-position, albeit with modest enantiomeric excess.[16] The DPA group on the nitrogen atom was selectively removed in a one-pot manner using 1-methylpiperazine, furnishing oxindole **3.35**. Recrystallization of oxindole **3.35** resulted in a satisfactory *ee* value of 92%.



[a]Reagents and conditions: (a) 1.15 eq NCS, 2.0 eq DABCO, DCM (0.1 M), -20 °C, 30 min, then 1.05 eq DPAOH, rt, 4 h, 88%; (b) 1.05 eq KOt-Bu, 1.2 eq 18-crown-6, THF (0.2 M), -78 °C to 0 °C, 30 min, then 1.3 eq 3-32, 0 °C, 18 h, 98%; (c) 2 mol% (*S*,*S*)-AcOLeDMAP, EtOAc (0.2 M), 0 °C, 36 h, then 2.0 eq 1-Me-piperazine, rt, 40 h, 88%, 78% ee; 76%, 92% ee after recrystallization.

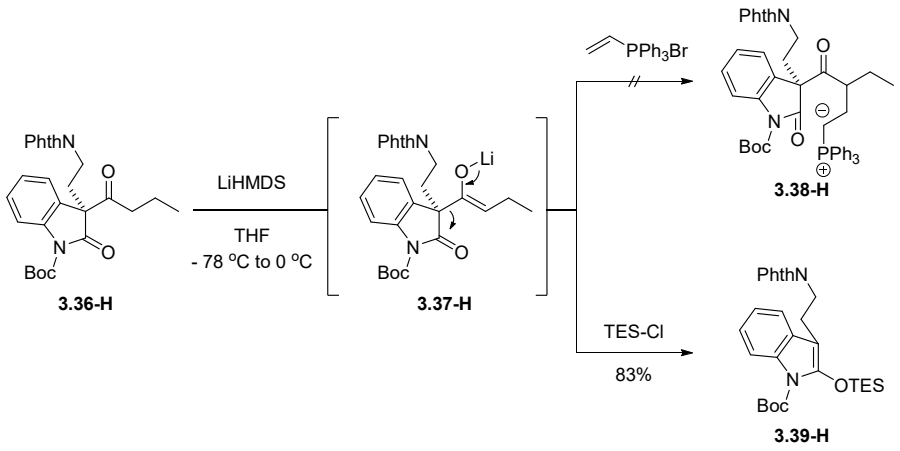
Scheme 3.6. Concise Synthesis of 3-Acyloxindole[a]

3.2.3. Construction of the C Ring

3.2.3.1. Top-Down Approaches

Having the dicarbonyl compounds in hand, the C ring cyclization using enolate chemistry was deemed worthwhile to investigate. The top-down approaches, where the reacting element was generated firstly from the upper carbonyl,

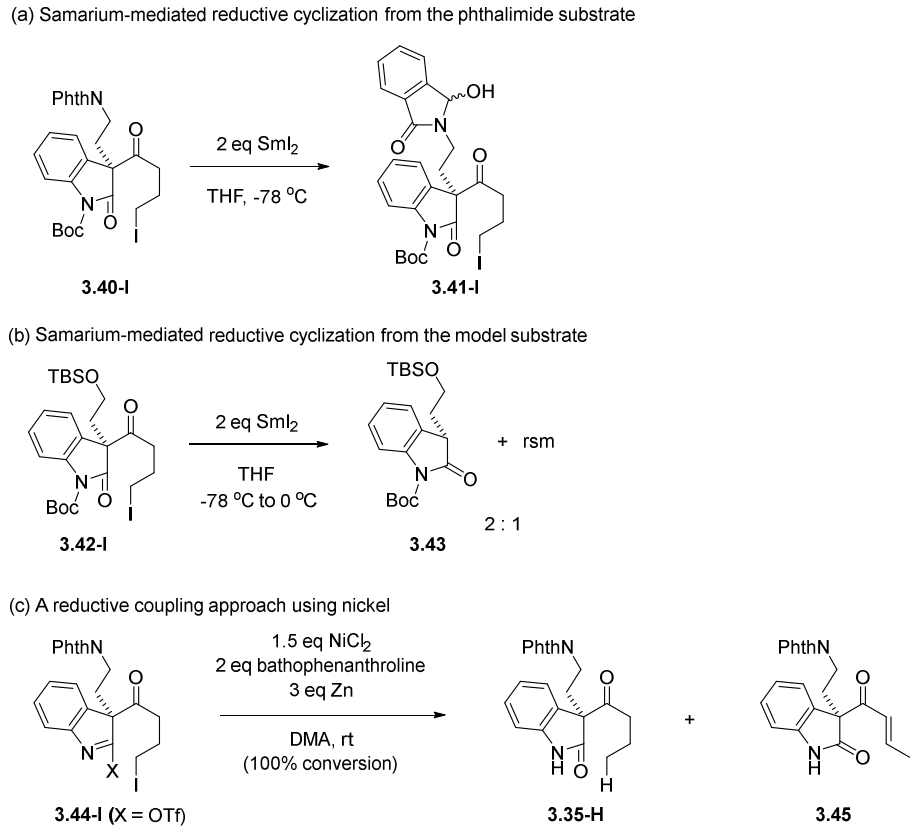
commenced with a use of the Schweiser reagent (Scheme 3.7). After treatment of *N*-Boc-protected dicarbonyl **3.36-H** with a strong base LiHMDS, triphenylvinylphosphonium bromide, the Schweiser reagent, was added to the mixture envisaging a sequence of the Michael addition and an intramolecular Wittig reaction from the resultant adduct **3.38-H**. However, instead of incorporating a two carbon unit, the reaction consistently led to loss of butanoyl group, implying enolate **3.37-H** was unstable even at –78 °C. In addition, quenching the reaction with chlorotriethylsilane afforded *O*–silyl oxindole **3.39-H** in good yield, attesting the existence of the formal retro-Claisen condensation pathway.



Scheme 3.7. The First Observation of the Retro-Claisen Condensation

It is this retro-Claisen condensation that hampers every attempt based on the top-down approaches. For example, a samarium-mediated reductive cyclization

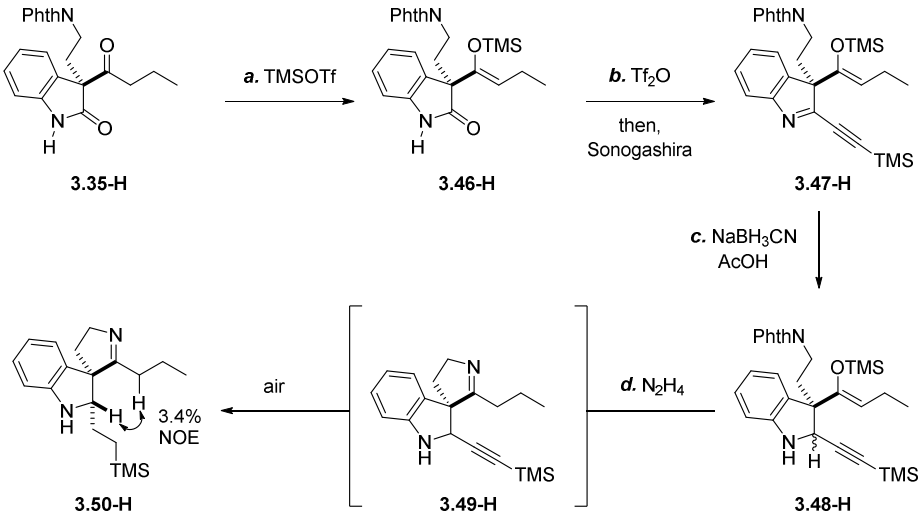
failed with the model substrate **3.42-I** giving only deacylated product **3.43**, presumably due to the labile nature of the 1,3-dicarbonyl moiety (Scheme 3.8b). While the phthalimide moiety was not inert in the samarium conditions (Scheme 3.8a), reductive coupling conditions using stoichiometric nickel from imidoyl triflate **3.44-I** did not ruin the phthalimide or the 1,3-dicarbonyl moiety (Scheme 3.8c). However, hydrolysis of the imidoyl triflate was fast to regenerate the oxindole moiety, also leading to simple reduction (cf. **3.35-H**) and elimination (cf. **3.45**), and no sign of the cyclization event was detected.



Scheme 3.8. The Top-Down Approaches: Reductive Cyclization

3.2.3.2. Bottom-Up Approaches: Early-Reduction

The oxindole moiety, adopted to set up the first stereogenic center, needed to be eliminated as early as possible, since the retro-Claisen condensation was consistently observed as discussed in the previous section. Thus, model studies were carried out using **3.35-H** in order to find manipulations compatible with carbonyl groups and the oxindole reduction route (Scheme 3.9).

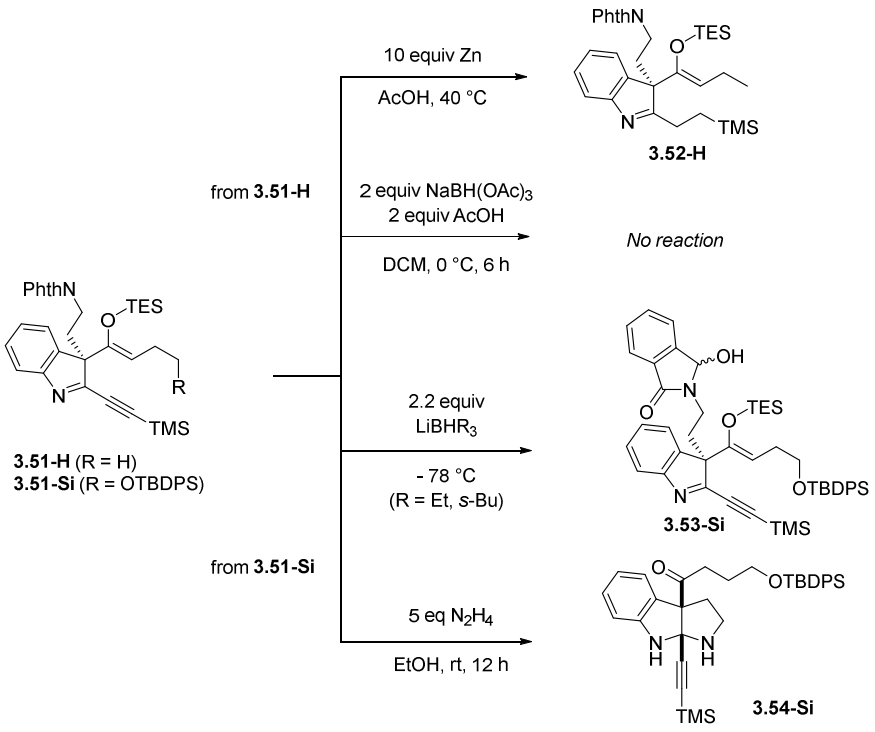


[a]Reagent and conditions: (a) 4 equiv TMSOTf, 6 equiv TEA, DCM (0.2 M), 0 °C, 24 h, 100%.; (b) 1.05 equiv Tf_2O, 1.2 equiv 2-fluoropyridine, DCM (0.1 M), -78 °C, 1.5 h, then, 6.0 equiv DIPEA, 4.0 equiv TMS-C≡CH, 5.0 mol% $Pd(PPh_3)_2Cl_2$, 10 mol% CuI, THF-DCM (0.05 M), rt, 6 h.; (c) 5 equiv $NaBH_3CN$, AcOH, 15 °C, 30 min.; (d) 5 equiv N_2H_4-H_2O, EtOH, 65 °C, air, 41% for 3 steps.

Scheme 3.9. Alkynylation and Reduction of Oxindole[a]

Susceptibility of the ketone toward nucleophiles was mitigated by converting to silyl enol ether **3.46-H**. After activation of the amide by triflic anhydride, the Sonogashira coupling reaction proved effective and highly reproducible, whereas reduction of the oxindole amide was problematic. Cyanoborohydride was found to reduce the imine functionality selectively in the presence of a phthalimide, affording indoline **3.48-H** as a 5:1 mixture of diastereomers. However, the major diastereomer had opposite stereochemistry at the indoline C2 position, which was confirmed by NOE experiments on **3.50-H** after phthalimide deprotection, condensation, and diimide reduction of the alkynyl group.

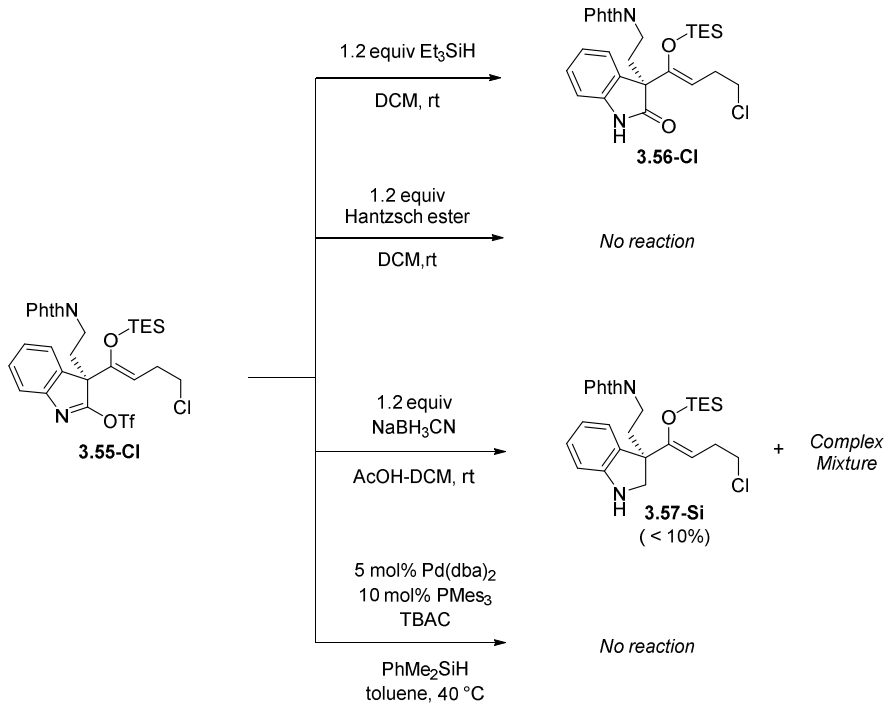
Additional screening experiments for the reducing agents were briefly carried out using ethynylimine substrates **3.51-H** and **3.51-Si** (Scheme 3.10). The metallic reduction using activated zinc in acetic acid reduced the C–C triple bond of **3.51-H** furnishing **3.52-H**. A mild borohydride, $NaBH(OAc)_3$, did not react with either the phthalimide or the alkynylimine. The bulkier and stronger reductants, such as L-Selectride® and Super-Hydride® failed to reduce the imine of **3.51-Si**, affording only phthalimide reduction product **3.53-Si**. In addition to the attempts toward the stereoselective reduction of imines, the *syn*-relationship between the silyl enol ether and the alkynyl groups could be transiently established by the formation of a bicyclic ring. However, while expected bicyclic ring formation was accompanied with the deprotection of the phthalimide moiety, the silyl enol ether became susceptible to the reaction conditions yielding desilylated ketone **3.54-Si**.



Scheme 3.10. Attempts toward the Reduction of C2 after Alkynylation

Investigated next was the feasibility of the reduction of the C2 position before the alkynylation (Scheme 3.11). The reaction of imidoyl triflate **3.55-Cl** with triethylsilane[17] furnished formal hydrolysis product **3.56-Cl**, while the use of Hantzsch ester as a reductant resulted in the full-recovery of the starting triflate **3.55-Cl**. The reaction with sodium cyanoborohydride gave a small amount of fully-reduced indoline **3.57-Cl** within a very messy reaction mixture. Lastly, by considering the reactivity of imidoyl triflates being similar to that of acid chlorides, the reduction conditions for acid chlorides were tested, only to obtain

no fruitful result. [18] Overall, the early-reduction of the C2 position was revealed to be challenging with both ethynylimines and imidoyl triflates.



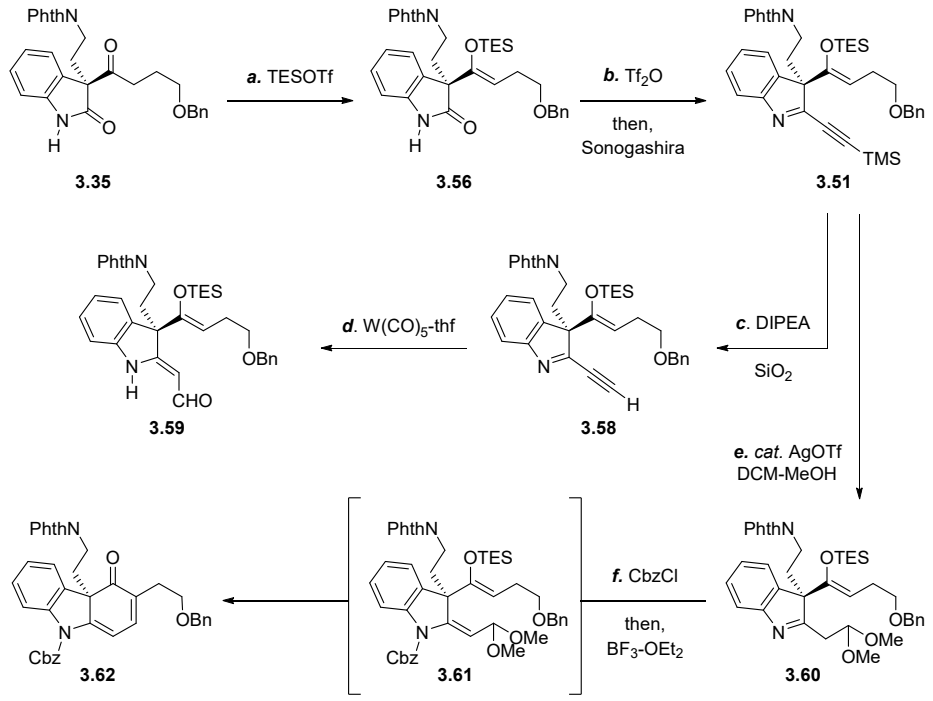
Scheme 3.11. Attempts toward the Reduction of C2 before Alkynylation

3.2.3.2. Bottom-Up Approaches: Early-Cyclization

At this stage, we changed our plan to make the cyclohexane ring first before adjusting the oxidation state at C2 position, since the fused-cyclic system may be advantageous for making a *cis*-junction (Scheme 3.12). A more robust triethylsilyl enol ether **3.56** was prepared from oxindole **3.35**, and subsequent amide triflation and Sonogashira coupling reactions afforded ethynyl imine

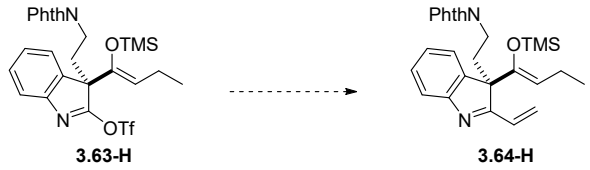
3.51. Filtration of trimethylsilylalkyne **3.51** through deactivated silica gel brought about selective desilylation of alkynyl TMS group. However, metal-vinylidene-mediated cyclization reactions failed with terminal alkyne **3.58**. For example, Iwasawa's tungsten-catalyzed conditions gave the 1,4-addition product **3.59**, presumably due to the susceptible nature of the ethynyl imine moiety toward nucleophilic attack of adventitious water.[19]

To construct the central cyclohexane ring, a more classical approach was pursued (Scheme 3.12). Treatment of silyl alkyne **3.51** with substoichiometric silver triflate in DCM–methanol cosolvent gave clean desilylation of the alkynyl TMS in the presence of TES–enol ether, whereas the conditions induced facile desilylation of a TMS–enol ether (cf. **3.46-H**). Concomitant double Michael addition in the silver conditions furnished acetal **3.60**, which was directly subjected to *N*-carbamoylation and Mukaiyama Aldol condensation to give rise to cyclohexadienone **3.62**.



[a]Reagent and conditions: (a) 4 equiv TESOTf, 6 equiv TEA, DCM (0.2 M), 55 °C, 48 h, 81% (97% brsm).; (b) 1.05 equiv Tf_2O, 1.2 equiv 2-fluoropyridine, DCM (0.1 M), -78 °C, 1.5 h, then, 6.0 equiv DIPEA, 4.0 equiv TMS-C≡CH, 5.0 mol% $Pd(PPh_3)_2Cl_2$, 10 mol% CuI, THF-DCM (0.05 M), rt, 6 h., 69%.; (c) DIPEA, SiO_2, 100%.; (d) 1 equiv $W(CO)_5$-thf, toluene, 80 °C, 24 h.; (e) 25 mol% AgOTf, DCM-MeOH (2:1, 0.1 M); (d) 1.2 equiv CbzCl, 2.0 equiv 2,6-lutidine, 0 °C to rt, 20 h, then 2.5 equiv BF_3-OEt_2, 0 °C, 6 h, 40% for 2 steps

Scheme 3.12. Non-Reductive Annulation of C-Ring[a]



	Vinyl-M (1.5 equiv)	Conditions	Products
Suzuki	KF_3B	5 mol% $PdCl_2$(dppf) i-PrOH, rt, 12 h	PhthN, N, H — **3.65-H** (54%); PhthN, O, N, H, O — **3.35-H** (15%)
Negishi	$Zn(\quad)_2$	5 mol% $Pd(PPh_3)_4$ 3 equiv TBAB THF, rt, 30 min	PhthN, OTMS, N — **3.66-H** (95%)
Lee	$BrMgIn(\quad)_4$	5 mol% $Pd(PPh_3)_2Cl_2$ 3 equiv TBAB THF, rt, 4 h	PhthN, OTMS, N — **3.64-H** (82%)

Scheme 3.13. Cross-Coupling Reactions of Imidoyl Triflate

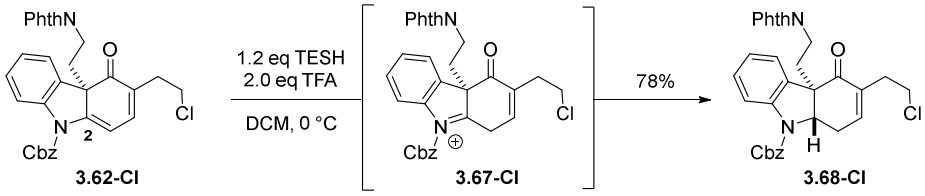
From a vantage point of a synthetic strategy, the installation of an alkynyl group is not necessary, since it no longer offers an opportunity for transition metal-catalyzed cyclization while requiring more steps for reduction. To overcome this inefficiency, vinylation of the imidoyl triflate was screened (Scheme 3.13). Suzuki-Molander conditions[20] employing a vinyltrifluoroborate reagent coupled the imidoyl and vinyl groups. However, the alcoholic solvent induced desilylation of silyl enol ether and subsequent deacylation, furnishing rearomatized indole **3.65**. The Organ's modification[21] of the Negishi reaction

was hard to control, as the subsequent 1,4-addition to the vinylimine product occurred with a much faster rate, producing **3.66-H** in excellent yield. The first clear observation of vinylimine **3.64-H** was made employing Lee's conditions,[22] where a tetraorganoindium magnesiate complex was used as the transmetallating reagent. However, the resulting vinyl imine **3.64-H** was unstable at ambient temperature, and a few attempts toward C-ring cyclization proved unsuccessful; addition of a Lewis acid caused faster degradation and *N*-carbamoylation using benzyl chloroformate (Cbz–Cl) was not feasible at low temperature.

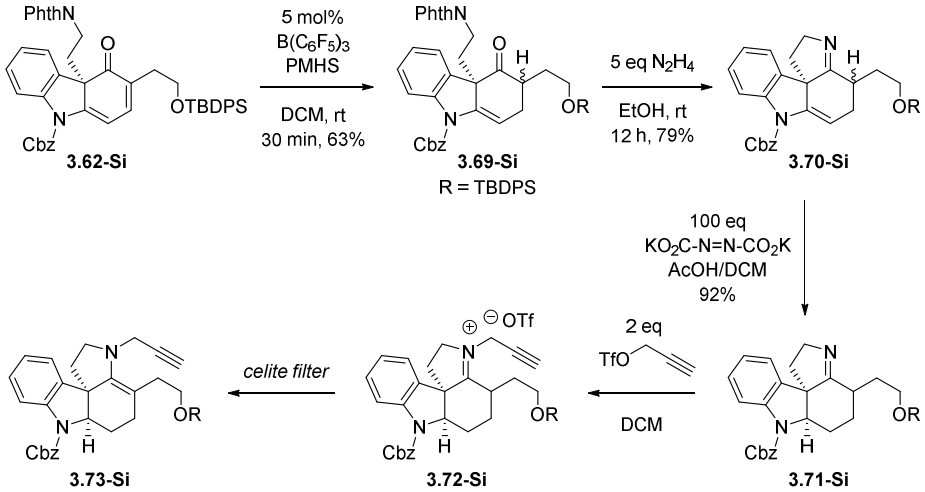
3.2.4. Construction of the D–E Ring System

Having the cyclohexadienone C ring in hand, reduction of C2 position became the highest priority. It is because when an sp^2-hybridized carbon was placed at C2, a ketone functionality is susceptible toward nucleophilic attack, and C–C bond cleavage was observed through a retro-Claisen and rearomatization pathway.

A silicon hydride reagent was found to be effective for the enamine reduction (Scheme 3.14). Treatment of the cyclohexadienone with triethylsilane and TFA gave rise to single diastereomer **3.68-Cl**, however, the stereochemistry of the indoline C2 position was to be of β–configuration.



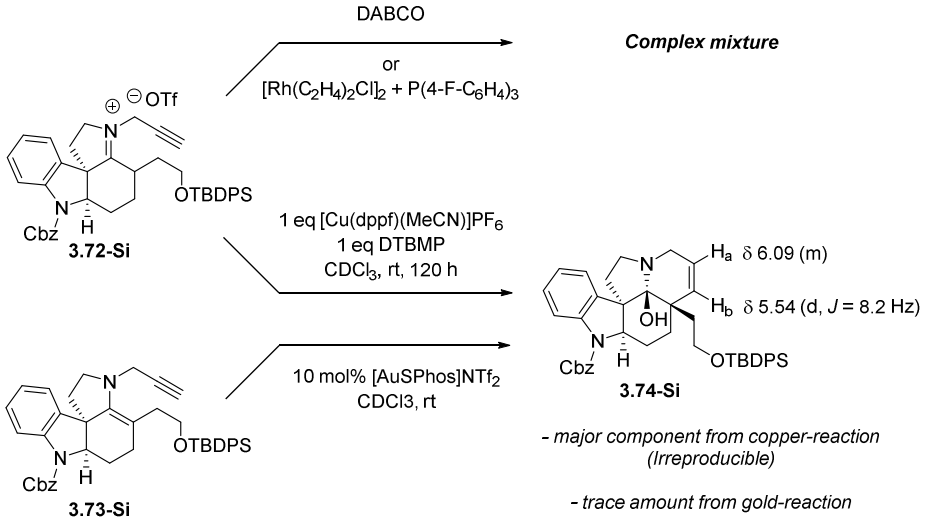
Scheme 3.14. Reduction of Cyclohexadienone Using Silicon Hydride



Scheme 3.15. Construction of A-B-C-D Tetracycle

We suspected that the α,β–unsaturation may influence the stereochemical outcome of the C2 reduction. While silane reduction in the presence of a strong Brønsted acid reduced enamine moiety, selective 1,4-reduction of enone could be achieved using a silicon hydride with $B(C_6F_5)_3$ catalyst (Scheme 3.15).[23] It should be pointed out that enamine **3.69-Si** was unstable in DCM/TFA medium, implying that the carbonyl group was stabilized by conjugation (cf. **3.67-Cl**). Tetracycle **3.70-Si**, obtained from phthalimide deprotection and concomitant

condensation, has large strain as the enamine and imine parts render six-membered ring system nearly flat while the pyrroline ring exerts torsional strain toward one direction. It is this strain that effects stereochemical outcome of the reduction of enamine **3.70-Si**, which upon treatment with diimide gave rise to the *cis*-fused indolinocyclohexane **3.71-Si**. Propargylation of imine **3.71-Si** smoothly took place with excess amount of propargyl triflate, furnishing **3.72-Si**. Tautomeric enamine **3.73-Si** could be observed after filtration through a pad of celite, although its stability was not good sufficient to carry out the next step.



Scheme 3.16. E-Ring Cyclization Mediated by Metal π-Alkyne Complex

Unfortunately, iminium **3.72-Si** was not compatible with an amine base or rhodium catalyst, the two crucial components for the propargyl enamine cycloisomerization (Scheme 3.16). When an equimolar amount of the Cu–dppf

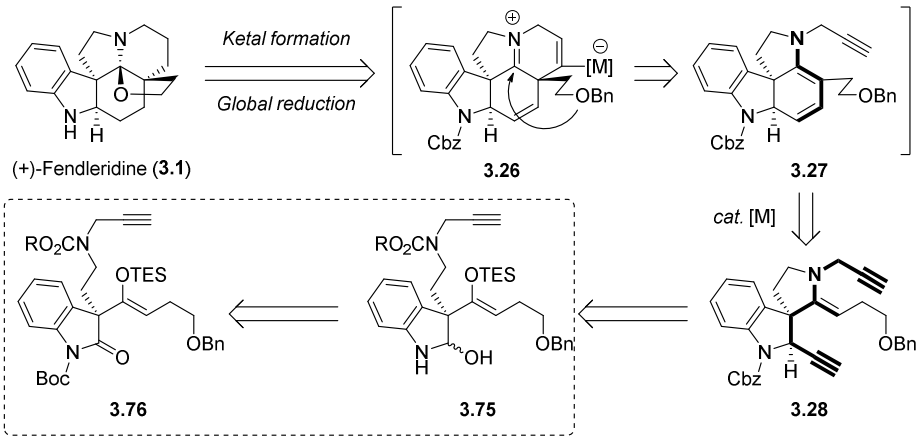
catalyst, a known alkyne π-activation catalyst,[24] was applied, formation of putative pentacycle **3.74-Si** was observed in a ^{1}H NMR monitoring study. However, the reaction was irreproducible, purportedly implying that some contaminant might have catalyzed the cyclization. In addition, when the unstable enamine **3.73-Si** was subjected to a gold catalyst, which was known for 6-endo cyclization reported by Barriault et al.,[25] a similar set of alkenyl peaks was observed in trace amount.

3.4. Conclusion and Future Plan

Enantioselective total synthesis of (+)-fendleridine has been pursued by using a transition-metal-catalyzed cascade cyclization approach. To prove the pivotal concept, cascade cyclization, a synthetic route to the *N*-propargyl iminium intermediate has been investigated. Oxidative carbonylation of indole based on *O*-to-*N* and *O*-to-*C* acyl migration chemistry has been firmly established. Construction of the six-membered carbocycle and -azacycle witnessed partial success.

A brief survey has been made to test the feasibility of enamine cycloisomerization at the late stage of the synthesis. A step-by-step synthesis appears to be a less promising strategy for the completion of the synthesis, since the in situ preparation of the final enamine intermediate is needed. As our primary goal is demonstration of the strategic utility of metal-vinylidene-catalysis, revisiting the original retrosynthetic plan will be the next step.

If the first alkynylation at C2 occurs with desired stereochemistry, the overall synthesis will be improved, with significant brevity available from the proposed cascade cyclization (Scheme 3.17). In addition, an initial cycloisomerization would afford conjugated enamine **3.27**, making the fully-substituted enamine more viable for the final cyclization process. To implement this strategy, the investigation on the feasibility of oxindole reduction and subsequent alkynylation at indole C2 position is currently undergoing.



Scheme 3.17. Revisiting the Original Strategy: The Future Plan

3.5. References

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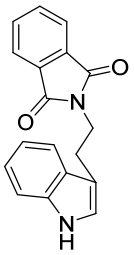
3.6. Experimental Sections

3.5.1. General Information

Anhydrous solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour. Yields refer to spectroscopically pure compounds unless otherwise stated. The progress of reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 ml of concentrated sulfuric acid in 250 ml of ethanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 mL of 5% NaOH solution

in 300 mL of water), or a cerium ammonium molybdate solution (2.5 g of ammonium molybdate tetrahydrate, 1.0 g of cerium ammonium sulfate dehydrate, 10 mL of sulfuric acid in 90 mL water). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60). Commercially available reagents were purchased from Sigma-Aldrich, Strem, TCI, Acros, or Alfa Aesar. NMR spectra were obtained on a Bruker DPX-300 (300 MHz), an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million (δ) relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz (Hz). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High performance liquid chromatography data and mass spectra were obtained on a Shimadzu LCMS-2020 (LC-20AD pump, SPD-20A UFLC version UV-VIS detector, LCMS-2020 mass spectrometer, ∝CTA-20A column oven, FRC-10A fraction collector), Thermoscientific Syncronis C18 column (ID 4.6 mm, 5 μm particle size, 150 mm length) system. Unless otherwise stated, HPLC system was operated under binary solvent system (A = acetonitrile/TFA 99.9:0.1, B = H_2O/TFA 99.9:0.1), flow rate 1.0 ml/min, column temperature 40 ºC. Gas chromatography data were obtained on a Hewlett Packard HP 6890 Series GC system.

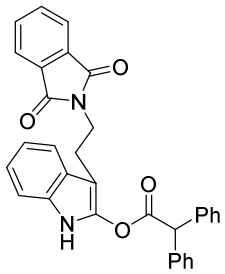
3.5.2. Experimental Procedure and Characterization Data



2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dionesolution (3.30)

Phthalimide **3.30** was prepared according to literature procedure,[1] with a modification. To a two-neck flask equipped with reflux condenser were added tryptamine (6.308 g, 40 mmol), phthalic anhydride (6.440 g, 44 mmol), and toluene-THF (400 mL, 7:3). The flask was charged with nitrogen gas and evacuated for three times. The mixture was refluxed for 14 hours and allowed to cool down to ambient temperature. The crude mixture was concentrated *in vacuo* and re-dissolved in DCM. After filtration through silica gel (DCM-EA 1:1), filtrate was concentrated and recrystallized from DCM/hexane to give **3.30** (10.881 g, 98%) as a yellow solid. Spectroscopic data was in good agreement with reported data.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.73 (d, *J* = 6.6 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.15 – 7.07 (m, 2H), 4.00 (dd, *J* = 8.7, 6.9 Hz, 2H), 3.17 – 3.12 (m, 2H).

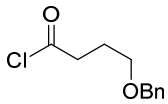


3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-2-yl diphenylacetate (3.31)

To a flame-dried round-bottom flask were added **3.30** (5.2368 g, 18 mmol), DABCO (4.0380 g, 36 mmol) and DCM (180 mL) under argon atmosphere. The solution was cooled down to – 20 °C, and *N*-chlorosuccinimide (2.7641 g, 20.7 mmol) was added to the mixture in five portions. After stirring at this

temperature for 30 min, the mixture was moved to ice-water bath, and diphenylacetic acid (4.0113 g, 18.9 mmol) was added in one portion. The mixture was allowed to reach to room temperature and stirred for 4 hours. Dichloromethane solvent was evaporated until total volume of the mixture reached to *ca.* 50 mL, and poured into EtOAc (300 mL). Organic phase was washed with water (100 mL), HCl (0.5 M, 100 mL), water (100 mL), sat. $NaHCO_{3(aq)}$ (100 mL) and brine, then dried over anhydrous $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on SiO_2 gave **3.31** (7.7809 g, 88%) as a yellow solid. (Note that the nearest byproduct is an *O*-to-*N* acyl-migration product, and can be used as mixture with **3.31** in next step.)

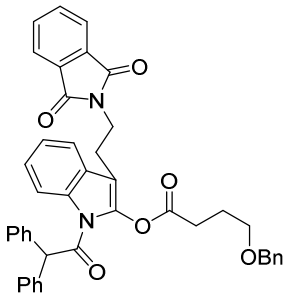
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (m, 1H), 7.77 (m, 2H), 7.67 (d, *J* = 6.7 Hz, 1H), 7.60 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* =5.5 Hz, 1H), 7.31 (m, 2H), 5.32 (s, 1H), 3.90 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H).; ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.27, 168.23, 140.11, 137.60, 133.80, 132.14, 131.41, 128.89, 128.75, 127.71, 126.28, 123.09, 121.87, 120.16, 118.50, 111.10, 96.77, 56.87, 37.54, 22.09.



4-(benzyloxy)butanoyl chloride (3.32)

To a solution of 4-(benzyloxy)butanoic acid[2] (2.9154 g, 15 mmol) and 2,6-lutidine (1.9 mL, 16.5 mmol) in toluene (150 mL) was added thionyl chloride (1.2 mL, 16.5 mmol) rapidly at 0 °C (Note that dropwise addition may induce acid anhydride formation). After stirring at 0 °C for 4 h, all the volatiles were evaporated. The resulting mixture was triturated with Et_2O, and filtered through a pad of $Na_2SO_{4(s)}$. Evaporation of the crude material gave **3.32** (2.5475 g, 80%) as a brown oil, which was used directly for next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 4.49 (s, 2H), 3.51 (t, *J* = 5.4 Hz, 2H), 3.03 (t, *J* = 7.2, 1H), 2.04 – 1.95 (m, 2H).

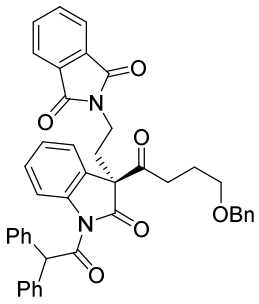


3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-(2,2-diphenylacetyl)-1H-indol-2-yl 4-(benzyloxy)butanoate (3.33)

To a solution of **3.31** (3.0022 g, 6 mmol) and 18-crown-6 (1.7446 g, 6.6 mmol) in THF (30 mL, 0.2 M) was added potassium *tert*-butoxide solution (6.3 mL, 1 M in THF, 6.3 mmol) at -78 ^{0}C under nitrogen atmosphere. The solution was immediately turned into deep purple color upon addition of KO*t*-Bu. After stirring at this temperature for 2 h, acid chloride **3.32** (1.5312 g, 7.2 mmol) was added to the mixture at -78 ^{o}C. The solution was leaved to stir at -78 ^{o}C overnight, and another 4 h at 0 ^{o}C. The reaction was quenched with 1 N HCl (10 mL) and reaction color turned into pale yellow. Aqueous layer was extracted with Et_2O three times and the combined organic phase was washed with water, sat. $NaHCO_{3(aq)}$, and brine, and dried over anhydrous $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on SiO_2 gave **3.33** (3.8818 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H), 7.80 (dd, *J* = 5.0, 3.2 Hz, 2H), 7.72 – 7.64 (m, 3H), 7.36 – 7.11 (m, 17H), 5.83 (s, 1H), 4.50 (s, 2H), 3.91 – 3.85 (m, 2H), 3.49 (t, *J* = 5.9 Hz, 2H), 2.85 – 2.78 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.90 – 1.81 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.76,

170.68, 168.04, 139.05, 138.41, 137.71, 133.92, 133.19, 132.14, 129.08, 128.69, 128.36, 127.63, 127.58. 127.40, 127.29, 125.12, 124.03, 123.18, 118.54, 116.22, 106.33, 72.80, 68.69, 58.50, 36.26, 30.30, 24.51, 22.22.

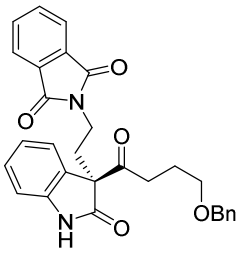


(*S*)-2-(2-(3-(4-(benzyloxy)butanoyl)-1-(2,2-diphenylacetyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (3.34)

To a solution of **3.33** (3.6563 g, 5.4 mmol) in EtOAc (27 mL, 0.2 M) was added a pre-cooled solution of (S,S)-AcOLeDMAP (21.1 mg, 0.55 mmol) [3] in EtOAc (2.7 mL) at 0 ºC. The mixture was stirred for 48 hours at 0 ºC and quenched with 1N HCl solution, and poured into Et_2O. The organic layer washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Crude mixture (3.1476 g, 86%) was pure enough to conduct next step without purification and flash column chromatography induce deacylation of carbonyl at C3 position. Analytical sample was prepared by taking small portion of the crude mixture, and triturating from Et_2O/hexane. The combined aqueous phases were neutralized and extracted with DCM to recover (*S*,*S*)-AcOLeDMAP catalyst.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.59 (m, 4H), 7.40 – 6.92 (m, 18H), 6.55 (s, 1H), 4.23 (s, 2H), 3.54 (dt, *J* = 14.2, 7.2 Hz, 1H), 3.41 – 3.33 (m, 1H), 3.02 (t, *J* = 6.1 Hz, 2H), 2.73 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.59 – 2.48 (m, 1H), 1.68 (t, *J* = 5.8 Hz, 2H), 1.56 – 1.37 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.12, 174.40, 172.80, 167.54, 140.92, 138.03, 133.75,

131.67, 129.50, 129.34, 128.72, 128.39, 128.28, 127.50, 127.46, 127.38, 127.26, 125.72, 125.54, 123.07, 123.02, 116.98, 72.56, 68.34, 65.36, 58.12, 34.24, 33.22, 30.84, 23.12.; IR (neat): ν_{max} 1750.53, 1712.78, 1600.49, 1465.51, 1397.04, 1255.44, 1125.11 cm^{-1}.



(S)-2-(2-(3-(4-(benzyloxy)butanoyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (3.35)

To a solution of **3.34** (2.4117 g, 3.6 mmol) in MeCN (18 mL, 0.2 M) was added 1-methylpiperazine (0.48 mL, 4.3 mmol) under nitrogen atmosphere. The mixture was stirred for 18 hours at ambient temperature. The heterogenous reaction mixture was poured into EtOAc (900 mL) until the solution became homogeneous. The organic phase was washed thoroughly with 1N HCl solution, and neutralized using sat. $NaHCO_{3(aq)}$, dried over $MgSO_4$, and concentrated under reduced pressure. Recrystallization by slow diffusion from 30 mL of DCM and 20 mL of hexane gave **3.35** (1.4580 g, 82%, 92% *ee*) as a white colorless sticky oil.

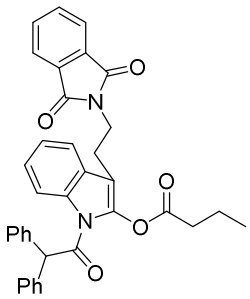
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (br s, 1H), 7.68 (dd, *J* = 5.4, 3.0 Hz, 1H), 7.59 (dd, *J* = 4.3, 3.2 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.16 (d, *J* = 7.1 Hz, 2H), 7.09 – 6.99 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 4.29 (s, 2H), 3.69 – 3.54 (m, 2H), 3.32 – 3.23 (m, 2H), 2.78 (dt, *J* = 15.0, 7.7 Hz, 1H), 2.66 – 2.50 (m, 2H), 2.32 (dt, *J* = 18.0, 7.0 Hz, 1H), 1.81 – 1.70 (m, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.67, 176.49, 167.78, 141.71, 138.30, 133.68, 131.83, 129.07, 128.23, 127.50, 127.41, 127.09, 123.77, 123.06, 122.95,

110.66, 72.63, 68.76, 65.38, 34.79, 33.73, 30.28, 23.46.; IR (neat): ν_{max} 3262.59, 2937.28, 1710.34, 1616.98, 1470.86, 1398.77, 1371.89, 718.65 cm^{-1}.; HPLC (Chiralpak IA, 4.6 mm × 250 mm, 75:25 hexane-isopropanol, 1.0 mL/min) T_R = 23.5 min (major), T_R = 31.0 min (minor).

One-pot procedure for the preparation of 3.35

To a solution of **3.33** (609.1 mg, 0.9 mmol) in EtOAc (4.5 mL, 0.2 M) was added a pre-cooled solution of (*S*,*S*)-AcOLeDMAP (3.5 mg, 0.009 mmol) in EtOAc (0.5 mL) at 0 °C. The mixture was stirred for 36 hours at 0 °C at which time 1-methylpiperazine (0.20 mL, 1.8 mmol) was added. After 48 hours at 0 °C, TLC indicated complete consumption of intermediate **3.34**. The reaction was quenched with 1N HCl solution, and poured into EtOAc (250 mL). The organic layer washed with water and brine, dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave Crude **3.35** (419.0 mg, 96%, 78% *ee*), which was subjected to recrystallization from DCM/hexane.

Experimental Procedures and Partial Characterization of S3.1, S3.2, 3.35-H, 3.46-H, and 3.50-H

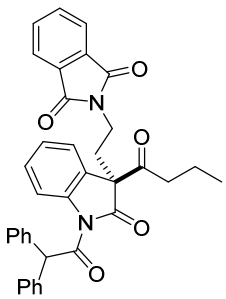


3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-(2,2-diphenylacetyl)-1H-indol-2-yl butyrate (S3.1)

To a solution of **3.1** (1.8400 g, 1.0 equiv) and 18-crown-6 ether (987.9 g, 1.1 equiv) in THF (40 mL) was added ^{t}BuOK (3.9 mL, 1.0 M in THF, 1.1 equiv)

slowly at 0 °C under nitrogen atmosphere. After stirring for 30 min, butyryl chloride (0.5 mL, 1.3 equiv) was added at 0 °C and the mixture was stirred for another 12 hours before quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with ethers two times. Combined organic layers were washed with brine, dried over $MgSO_{4(s)}$, and concentrated under reduced pressure. Flash column chromatography on silica gel provided desired relay-acylated product **S3.1** as a sticky oil (1.9278 g, 92%).

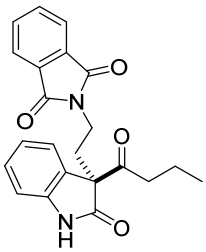
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, *J* = 6.8, 1.9 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.74 – 7.69 (m, 2H), 7.69 – 7.64 (m, 1H), 7.34-7.25 (m, 8H), 7.21 – 7.16 (m, 4H), 5.81 (s, 1H), 3.93 – 3.81 (m, 2H), 2.85 – 2.78 (m, 2H), 2.21 (t, *J* =7.5 Hz, 2H), 1.59 – 1.47 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).



2-(2-(3-butyryl-1-(2,2-diphenylacetyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (S3.2)

To a solution of **S3.1** (2.6710 g, 1.0 equiv) in $CHCl_3$ (78 mL) was added DMAP (57.5 mg, 0.1 equiv) at room temperature. After stirring for 30 min, the mixture was concentrated to *ca.* 10 mL volume under reduced pressure. The mixture was filtered through a short pad of silica flushed with Et_2O:Hexane:$CHCl_3$ (2:2:1). The filtrate was concentrated and recrystallized from $CHCl_3$/Et_2O affording rearranged product **S3.2** as a white solid (2.3897 g, 90%).

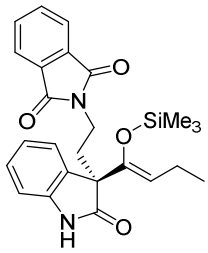
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.59 (m, 4H), 7.38 – 7.20 (m, 10H), 7.10 (t, *J* = 8.2 Hz, 1H), 7.04 (d,*J* = 6.4 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.57 (s, 1H), 3.86 (dt, *J* = 14.9 Hz, 9.7 Hz, 1H),3.41 (dt, *J* = 14.9 Hz, 9.7 Hz, 1H), 2.74 (dt, *J* = 14.9 Hz, 7.6 Hz, 1H), 2.55 (dt, *J* = 14.5 Hz, 6.0 Hz, 1H), 1.57 (dt, *J* = 18.1 Hz, 6.9 Hz, 1H), 1.44 (dt, *J* = 18.1 Hz, 7.0 Hz, 1H), 1.23-1.10 (m, 2H), 0.45 (t, *J* = 7.4 Hz, 3H).



2-(2-(3-butyryl-2-oxindole-3-yl)ethyl)isoindoline-1,3-dione (3.35-H)

To a solution of *C*-acyl oxindole **S3.2** (537.6 mg, 1.0 equiv) dissolved in MeCN (5.0 mL) was added Et_2NH (2.0 mL, 20 equiv) at room temperature. The mixture was stirred for 4 h at 50 °C and concentrated *in vacuo*. Flash column chromatography on silica gel afforded desired *N*-deprotected product **3.35-H** as colorless oil which turned to white solid upon standing at -20 °C (357.4 mg, 98%).

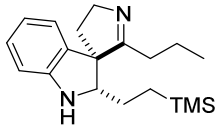
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (s, 1H), 7.73-7.55 (m, 4H), 7.08 – 6.99 (m, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 3.71 – 3.51 (m, 2H), 2.86 – 2.73 (m, 1H), 2.65 – 2.54 (m, 1H), 2.44 (dt, *J* = 17.7 Hz, 7.0 Hz, 1H),2.18 – 2.05 (m, 1H), 1.45 (qt, *J* = 14.0 Hz, 6.9 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H).



(Z)-2-(2-(3-(1-((trimethylsilyl)oxy)but-1-en-1-yl)-2-oxindole-3-yl)ethyl)isoindoline-1,3-dione (3.46-H)

To a flame-dried round-bottom flask was added solution of oxindole **3.35-H** (111.7 mg, 1.0 equiv) dissolved in DCM (3.0 mL), TEA (0.45 mL, 10 equiv) and TMSOTf (0.19 mL, 3.0 equiv) sequentially under argon atmosphere at 0 ^{o}C. The mixture was stirred for 24 h at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The biphasic mixture was diluted with ethyl acetate (20 mL) and the organic phase was washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on a short pad of silica gel afforded desired TMS-enolether **3.46-H** as a colorless oil which was further purified by recrystallization from $CHCl_3$/hexane (white needle, 134.6 mg, 100%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ8.71 – 8.42 (br s, 1H), 7.74 – 7.67 (m, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.02 (td, *J* = 7.7, 1.2 Hz, 1H), 6.87 – 6.74 (m, 2H), 4.78 (t, *J* = 6.8 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.55 (dt, *J* = 13.7, 7.8 Hz, 1H), 2.39 – 2.29 (m, 1H),2.07 – 1.83 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H), -0.09 (s, 9H).; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 179.62, 167.90, 147.38, 141.88, 133.66, 131.90, 130.86, 128.21, 124.26, 122.94, 122.20, 111.23, 110.26, 77.25, 57.34, 34.13, 31.84, 19.46, 14.11, 0.41.

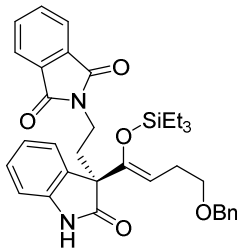


2'-propyl-2-(2-(trimethylsilyl)ethyl)-4',5'-dihydrospiro[indoline-3,3'-pyrrole] (3.50-H)

To a solution of oxindole **3.46-H** (22.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL) was added 2-fluoropyridine (5.1 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (52 μL, 1.0 M in DCM, 1.05 equiv) sequentially under argon atmosphere at -78 °C. After stirring for 20 min, the mixture was allowed to warm to 0 °C and stirred for another 30 min at 0 °C before quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and roughly concentrated *in vacuo* (caution: It decomposed upon full-concentration). The resulting triflate was re-dissolved in THF (0.5 mL). To the solution of the triflate were added $Pd(PPh_3)_4$ (5.8 mg, 0.1 equiv), CuI (1.2 mg, 0.1 equiv), ethynyltrimethylsilane (28 μl, 4.0 equiv), and DIPEA (52 μL, 6.0 equiv) sequentially under the constant flow of argon gas. The mixture was warmed up to 45 °C with pre-heated oil bath and stirred for 1 h. Then, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated under reduced pressure and re-dissolved in acetic acid (0.5 mL). To the mixture was added sodium cyanoborohydride (15.7 mg, 5.0 equiv) in one portion at 15 °C. After stirring for 30 min, the mixture was quenched with aqueous ammonia solution (1.0 mL) and further ammonia solution was added until pH was adjusted to 8-9. The aqueous layer was extracted with DCM (5 mL 3) and combined organic layer were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was re-dissolved in ethanol (0.5 mL) and hydrazine hydrate (20 μl, 5.0 equiv) was added to the mixture. The mixture was stirred for 4 h at 65 °C under ambient atmosphere before concentrated to dryness. The crude mixture was further concentrated three times with toluene. The resulting solid was filtered and the solid was washed with chloroform. The filtrate was concentrated under reduced

pressure and subjected to a flash column chromatography on silica gel affording pyroline **3.50-H** as a yellow oil (6.3 mg, 41%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (td, *J* = 7.7, 1.2 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.74 – 6.70 (m, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.86 – 3.77 (m, 1H), 3.73 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.46 (ddd, *J* = 13.5, 8.2, 5.5 Hz, 1H), 2.33 – 2.16 (m, 2H), 1.83 – 1.76 (m, 1H), 1.74 – 1.53 (m, 3H), 1.49 (tt, *J* = 13.4, 4.3 Hz,1H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.60 (td, *J* = 13.6, 4.6 Hz, 1H), 0.42-0.34 (m, 1H), 0.00 (s, 9H).; IR (neat): ν_{max}3362, 2954, 2871, 1636, 1606, 1484, 1466, 1248, 862, 836, 742 cm^{-1}

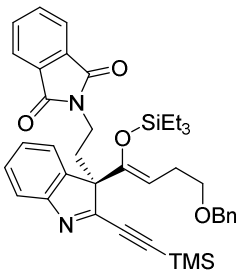


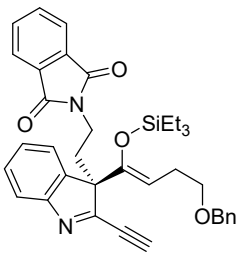
(*Z*)-2-(2-(3-(4-(benzyloxy)-1-((triethylsilyl)oxy)but-1-en-1-yl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (3.56)

To a sealed-tube containing a solution of **3.35** (2.8177 g, 5.84 mmol), TEA (5.0 mL, 35.8 mmol) in DCM (30 mL, 0.2 M) was added slowly triethylsilyl trifluoromethanesulfonate (5.4 mL, 23.8 mmol) under argon atmosphere at room temperature. After stirring 5 minutes at this temperature, the tube was tightly sealed with screw-cap and stirred for 48 hours at 45 °C. The reaction mixture was allowed to cool down to room temperature, and sat. $K_2CO_{3(aq)}$ (10 mL) was added (Caution: exothermic). After vigorous stirring for 4 hours at ambient temperature, phases were separated and aqueous phase was extracted with Et_2O three times. Combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography on SiO_2 afforded inseparable *E*/*Z* mixture (4:1)

of **3.56** (2.8831 g, 83%) as an orange sticky oil. Further elution from silica gel gave recovered starting material (462.9 mg, 16%). R_f 0.16 (hexane-EtOAc, 3:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.81 (m, 2H + 2H; *E* and *Z*, N-H), 7.73 – 7.65 (m, 2H + 2H; *E* and *Z*), 7.65 – 7.58 (m, 2H + 2H; *E* and *Z*), 7.33 – 7.17 (m, 4H + 5H; *E* and *Z*), 7.09 (d, *J* = 7.1 Hz, 1H; *E*), 7.04 – 6.97 (m, 1H + 1H; *E* and *Z*), 6.84 – 6.73 (m, 2H + 2H; *E* and *Z*), 4.83 (t, *J* = 6.9 Hz, 1H; *E*), 4.64 (t, *J* = 7.4 Hz, 1H; *Z*), 4.49 (s, 2H; *E*), 4.31 (s, 2H; *Z*), 3.67 (tdd, *J* = 13.7, 11.3, 6.7 Hz, 2H; *Z*), 3.56 (t, *J* = 7.2 Hz, 2H; *E*), 3.48 – 3.41 (m, 2H; *E*), 3.20 (ddd, *J* = 16.0, 12.5, 8.1 Hz, 2H; *Z*), 2.66 – 2.18 (m, 4H + 4H; *E* and *Z*), 2.14 – 2.05 (m, 1H; *Z*), 1.93 – 1.78 (m, 1H; *Z*), 0.97 (t, *J* = 7.9 Hz, 9H; *Z*), 0.87 – 0.67 (m, 9H + 6H; *E* and *Z*), 0.52 – 0.31 (m, 6H; *E*).; ^{13}C NMR (101 MHz, $CDCl_3$) δ; 179.25, 167.87, 167.79, 149.56, 148.17, 141.77, 138.52, 133.65, 133.60, 132.42, 132.03, 131.96, 130.89, 128.30, 128.17, 127.65, 127.50, 127.44, 127.30, 124.06, 122.94, 122.26, 110.13, 104.48, 77.36, 77.25, 77.04, 76.72, 72.79, 72.37, 69.99, 69.68, 60.53, 57.62, 34.08, 33.62, 32.08, 26.75, 25.97, 21.01, 14.12, 6.86, 6.78, 5.38, 4.99.





(*Z*)-2-(2-(3-(4-(benzyloxy)-1-((triethylsilyl)oxy)but-1-en-1-yl)-2-((trimethylsilyl)ethynyl)-3*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (3.51)

and

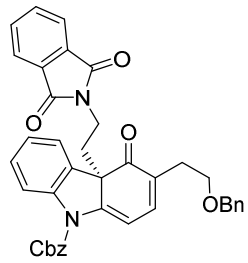
(*Z*)-2-(2-(3-(4-(benzyloxy)-1-((triethylsilyl)oxy)but-1-en-1-yl)-2-ethynyl-3H-indol-3-yl)ethyl)isoindoline-1,3-dione (3.58)

To a flame-dried round-bottom flask were added **3.56** (2.6851 g, 4.50 mmol), 2-fluoropyridine (0.46 mL, 5.4 mmol), and DCM (22.5 mL, 0.2 M). Trifluoromethanesulfonic anhydride (4.7 mL, 1 M in DCM, 4.7 mmol) was added to the mixture under argon atmosphere at -78 ^{o}C. After stirring 45 minutes at this temperature DIPEA (4.7 mL, 27 mmol) was added. The resulting deep-red solution was allowed to warm to ambient temperature. In an another flame-dried round-bottom flask were placed $PdCl_2(PPh_3)_2$ (157.9 mg, 0.23 mmol) and CuI (25.7 mg, 0.14 mmol). After evacuation and argon purge for three times, THF (22.5 mL) and ethynyltrimethylsilane (2.5 mL, 18 mmol) were added. The first reaction mixture containing an imidoyl triflate was cannulated to the second flask for Sonogashira reaction at ambient temperature. After 3.5 hours, the mixture was filtered through a pad of silica gel, flushed with Et_2O. Concentration under reduced pressure followed by flash column chromatography on SiO_2 afforded **3.51** (2.0838 g, 69%) as a brown oil. R_f 0.50 (hexane-EtOAc, 3:1). Desilylated ethynylimine **3.58** (388.3 mg, 12%) was isolated as a brown oil. R_f 0.38 (hexane-EtOAC, 3:1)

3.51 — ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 3.1 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.17 (m, 8H), 4.90 (t, *J* = 7.0 Hz, 1H), 4.61 (t, *J* = 7.3 Hz, 1H), 4.49 (s, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 3.32 – 3.22 (m, 1H), 3.05 – 2.94 (m, 1H), 2.52 – 2.25 (m, 4H), 0.72 (t, *J* = 7.9 Hz, 9H), 0.41 – 0.16 (m, 15H). ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.60, 166.86, 155.70, 148.69, 139.48, 138.44, 133.71, 133.65, 132.06, 132.02, 128.71, 128.31, 128.19, 127.61, 127.48, 126.96, 123.03, 122.76, 121.79, 107.04, 104.45, 97.75, 72.80, 69.74, 67.92, 33.33, 31.41, 26.83, 6.68, 5.35, -0.52.; IR (neat): ν_{max} 1715.3, 1453.3, 1397.2, 1369.4, 1088.0, 845.1, 733.4, 716.1 cm^{-1}.

3.58 — ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.64 – 7.57 (m, 3H), 7.34 – 7.15 (m, 8H), 4.92 (t, *J* = 6.8 Hz, 1H), 4.46 (s, 2H), 3.52 (s, 1H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.28 – 3.16 (m, 1H), 3.03 –

2.90 (m, 1H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.40 – 2.17 (m, 2H), 0.70 (t, *J* = 7.9 Hz, 9H), 0.37 – 0.16 (m, 6H).; IR (neat): ν_{max} 2954.7, 1773.1, 1714.55, 1398.6, 1370.5, 734.6, 716.6 cm^{-1}.; LC-MS (ESI) calcd. for $C_{37}H_{40}N_2O_4SiNa$ $[M+Na]^+$: 627.27, found: 627.20.



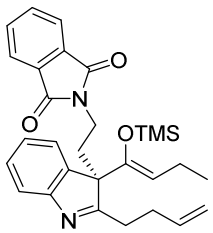
benzyl 3-(2-(benzyloxy)ethyl)-4a-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-oxo-4,4a-dihydro-*9H*-carbazole-9-carboxylate (3.62)

To a solution of **3.51** (1.6731 g, 2.47 mmol) in DCM-MeOH (13 mL, 6:4) was added AgOTf (192.5 mg, 0.75 mmol) at room temperature under argon atmosphere. Reaction progress was carefully monitored, because reaction times were not consistent over repetitions and prolonged reaction time caused decomposition of materials. After the starting materials were completely consumed, the reaction mixture was filtered through a pad of silica using Et_2O as an eluent (Caution: a celite pad need to be tightly packed. A residual silver complex induced vinyl ether formation during evaporation, rather than formation of the dimethoxyacetal). Concentration of filtrate gave crude acetal **3.60**, which was directly used in next step due to the poor stability.

In a flame-dried round-bottom flask was placed acetal **3.60** and the material was re-dissolved in DCM (13 mL, 0.2 M). To the solution were added 2,6-lutidine (0.44 mL, 3.75 mmol) and CbzCl (0.42 mL, 3.0 mmol) at 0 ^oC. After stirring at ambient temperature for 18 hours, the mixture was cooled down to 0 ^oC, and boron trifluoride diethyl etherate (0.46 mL, 3.75 mmol) was added to the mixture. After 6 hours of stirring at 0 ^oC, the reaction was quenched with sat. $NaHCO_{3(aq)}$ solution. Phases were separated and aqueous solution was

extracted with EtOAc three times. The combined organic layers were washed with water, brine, and dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography on SiO_2 afforded **3.62** (632.5 mg, 40%) as a bright yellow oil. R_f 0.18 (hexane-EtOAc, 4:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 4.8, 3.2 Hz, 2H), 7.64 – 7.59 (m, 2H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.31 – 7.20 (m, 5H), 7.20 – 7.12 (m, 2H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.49 (d, *J* = 6.7 Hz, 1H), 5.40 (q, *J* = 12.1 Hz, 2H), 4.49 (s, 2H), 3.74 – 3.63 (m, 1H), 3.62 – 3.50 (m, 3H), 2.74 – 2.63 (m, 1H), 2.62 – 2.51 (m, 1H), 2.31 (dt, *J* = 15.5, 7.4 Hz, 1H), 2.23 – 2.11 (m, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.58, 167.57, 154.22, 151.25, 141.14, 138.56, 135.01, 133.82, 131.96, 128.81, 128.70, 128.62, 128.49, 128.22, 127.57, 127.35, 126.66, 125.57, 124.23, 123.04, 115.66, 103.29, 72.75, 69.01, 68.68, 59.80, 41.47, 33.44, 29.41.; IR (neat): ν_{max} 1713.2, 1665.9, 1643.7, 1463.4, 1395.6, 1359.6, 1203.4, 751.9, 720.0 cm^{-1}.; LC-MS (ESI) calcd. for $C_{39}H_{32}N_2O_6Na$ $[M+Na]^+$: 647.22, found: 647.15.

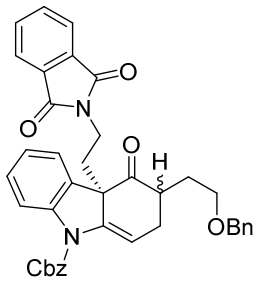


(*Z*)-2-(2-(2-(but-3-en-1-yl)-3-(1-((trimethylsilyl)oxy)but-1-en-1-yl)-3H-indol-3-yl)ethyl)isoindoline-1,3-dione (3.66-H)

To a flame-dried round-bottom flask was added a solution of oxindole **3.35-H** (179.4 mg, 1.0 equiv) dissolved in DCM (4.0 mL). 2-fluoropyridine (41μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (420μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78

°C. After stirring for 20 min, the mixture was allowed to warm to 0 °C and stirred for 30 min at 0 °C before quenched with saturated aqueous $NaHCO_3$solution (5 mL). The biphasic mixture was extracted twice with ether (10 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was re-dissolved in a small amount of THF (1.0 mL). To the solution of triflate were added $Pd(PPh_3)_4$ (23.1 mg, 0.05 equiv), tetrabutylammonium bromide (386.8 mg, 3.0 equiv), and divinylzinc (3.2mL,0.25 M in THF, 2.0 equiv) sequentially under constant flow of argon gas. After stirring for 12 h at room temperature, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated in vacuo, and directly subjected to a flash column chromatography on silica gel (hexane-EtOAc = 4:1) affording indole **3.66-H** as an yellow oil (191.2 mg, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ7.84 – 7.80 (m, 2H), 7.79 – 7.73 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.17 – 6.02 (m, 1H), 5.22 (d, *J* = 18.4 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 4.91 (t, *J* = 6.2 Hz, 1H), 3.08 – 2.91 (m, 2H), 2.82 – 2.69 (m, 4H), 2.50 – 2.40 (m, 1H), 2.35 – 2.24 (m, 1H), 2.20 – 2.08 (m, 1H), 2.04 – 1.95 (m, 1H), 1.03 (t, *J* = 7.4 Hz, 3H), -0.52 (s, 9H).; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 186.70, 167.95, 156.47, 148.15, 139.78, 138.24, 134.01, 132.09, 128.69, 125.48, 123.24, 122.84, 120.45, 115.03, 111.15, 77.33, 66.25, 33.38, 31.16, 30.02, 28.97, 19.57, 14.40, 0.18.

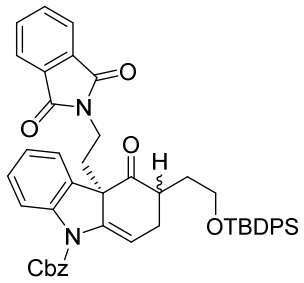


benzyl 3-(2-(benzyloxy)ethyl)-4a-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-oxo-2,3,4,4a-tetrahydro-9*H*-carbazole-9-carboxylate (S3.3)

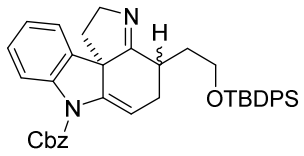
To a solution of **3.62** (437.3 mg, 0.7 mmol) and polymethylhydrosiloxane (210 μL, 3.50 mmol) in DCM (7.0 mL, 0.1 M) was added tris(pentafluorophenyl)borane solution dissolved in DCM (3.6 mg, 0.007 mmol, 0.07 mL DCM) at room temperature. After 30 minutes at ambient temperature, TLC monitoring indicated complete consumption of the starting materials. The reaction mixture was filtered through a short pad of silica gel eluting with Et_2O, and concentrated *in vacuo*. Flash column chromatography on SiO_2 afforded a 2.5:1 diastereomeric mixture of **S3.3** (159.6 mg, 36%) as a pale-yellow oil.

Partial characterization of S3.3 was supported by 3.62-Si, which was synthesized an analogous manner

S3.3 — ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.69 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.66 – 7.60 (m, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.31 (m, 4H), 7.28 (d, *J* = 4.6 Hz, 2H), 7.23 – 7.11 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.51 (br s, 1H), 5.39 (d, *J* = 12.2 Hz, 1H), 5.29 (d, *J* = 12.2 Hz, 1H), 4.47 (q, *J* = 12.0 Hz, 2H), 4.32 (dd, *J* = 28.0, 12.0 Hz, 0.74 H, *minor diastereomer*), 3.69 – 3.57 (m, 2H), 3.57 – 3.33 (m, 2H), 2.71 – 2.47 (m, 2H), 2.46 – 2.21 (m, 3H), 1.99 (ddd, *J* = 13.9, 9.6, 5.0 Hz, 1H), 1.86 – 1.73 (m, 1H).; ^{13}C NMR ***of the diastereomeric mixture*** (101 MHz, $CDCl_3$) δ 210.25, 167.69, 152.16, 140.37, 138.29, 135.47, 133.78, 131.89, 128.70, 128.59, 128.46, 128.36, 128.29, 128.25, 128.15, 127.59, 127.51, 127.48, 127.39, 125.45, 124.06, 123.01, 115.23, 108.38, 72.78, 68.02, 67.72, 57.19, 42.09, 33.56, 33.16, 30.93, 26.52.; IR (neat): ν_{max} 1773.1, 1714.1, 1464.8, 1395.3, 1351.2, 1073.4, 751.8, 718.0 cm^{-1}.; LC-MS (ESI) calcd. for $C_{39}H_{34}N_2O_6Na$ $[M+Na]^+$: 649.23, found: 649.15.



3.69-Si (Partial characterization) — ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.3 Hz, 2H), 7.69 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.63 (d, *J* = 5.8 Hz, 6H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.44 – 7.29 (m, 8H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.47 (d, *J* = 6.3 Hz, 1H), 5.41 (d, *J* = 12.2 Hz, 1H), 5.31 (d, *J* = 12.2 Hz, 1H), 3.88 – 3.71 (m, 2H), 3.60 – 3.48 (m, 1H), 3.46 – 3.37 (m, 1H), 2.64 – 2.51 (m, 1H), 2.49 – 2.25 (m, 3H), 2.08 – 1.97 (m, 1H), 1.64 – 1.51 (m, 1H), 1.01 (s, 9H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.50, 167.70, 152.19, 140.86, 140.36, 135.53, 135.51, 133.79, 133.68, 133.58, 131.88, 129.63, 128.71, 128.59, 128.47, 128.38, 128.35, 127.65, 125.52, 124.06, 123.01, 115.24, 108.29, 68.04, 61.40, 57.21, 41.49, 34.20, 33.56, 32.93, 26.86, 26.52, 19.16.

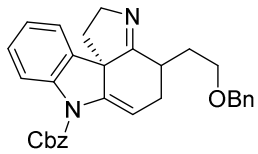


benzyl (11bR)-4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1,2,4,5-tetrahydro-7H-pyrrolo[2,3-d]carbazole-7-carboxylate (3.70-Si)

To a flame-dried screw-capped 5 mL vial were added **3.69-Si** (155.0 mg, 0.20 mmol), EtOH (2.0 mL, 0.10 M), and hydrazine monohydrate (49 μL, 1.0 mmol) at room temperature. The solution was bubbled with argon for approximately 30 seconds, and equipped with screw-cap. After stirring for 18 hours, the mixture was filtered through glass fibers. The crude mixture was concentrated

in vacuo, and subjected to flash column chromatography on silica gel affording **3.69-Si** (74.6 mg, 56%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.59 (dd, *J* = 6.3, 4.1 Hz, 4H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.44 – 7.19 (m, 10H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.05 (br s, 1H), 5.37 (dd, *J* = 37.3, 12.2 Hz, 2H), 3.92 – 3.73 (m, 4H), 2.45 (ddd, *J* = 13.0, 9.9, 5.4 Hz, 2H), 2.29 (dt, *J* = 19.3, 5.9 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.94 (dd, *J* = 13.9, 6.1 Hz, 2H), 1.72 (td, *J* = 13.2, 6.5 Hz, 2H), 0.96 (s, 9H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.19, 152.09, 145.32, 135.71, 135.48, 133.90, 133.86, 132.14, 129.48, 128.67, 128.42, 128.34, 128.13, 127.55, 123.22, 120.69, 115.44, 111.88, 67.76, 61.86, 60.26, 56.38, 43.50, 37.21, 32.38, 32.26, 26.83, 19.17.

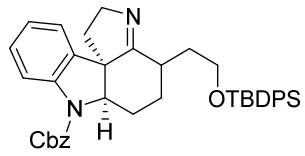


Benzyl-4-(2-(benzyloxy)ethyl)-1,2,4,5-tetrahydro-7*H*-pyrrolo[2,3-d]carbazole-7-carboxylate (S3.4)

S3.4 (67.4 mg, 70%) was synthesized starting from **S3.3** (124.7 mg, 0.20 mmol), in an analogous manner to **3.70-Si**.

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.33 – 7.21 (m, 6H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.11 (br s, 1H), 5.39 (dd, *J* = 42.1, 12.2 Hz, 2H), 4.48 (q, *J* = 12.0 Hz, 2H), 3.88 (d, *J* = 8.7 Hz, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.51 (dd, *J* = 15.2, 7.4 Hz, 2H), 2.35 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.13 (dd, *J* = 20.6, 10.2 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.80 (dd, *J* = 13.8, 6.4 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl^3$) δ 183.11, 152.08, 145.43, 140.47, 138.53, 135.75, 132.15, 128.68, 128.41,

128.29, 128.19, 127.59, 127.45, 123.24, 120.67, 115.52, 111.84, 72.93, 68.13, 67.78, 60.35, 56.42, 43.51, 37.58, 32.30, 29.69.; IR (neat): ν_{max} 2865.8, 1714.3, 1472.3, 1461.0, 1398.6, 1351.3, 1306.3, 1106.8, 751.6, 698.0 cm^{-1}.; LC-MS (ESI) calcd. for $C_{31}H_{31}N_2O_3$ $[M+H]^+$: 479.23, found: 479.20

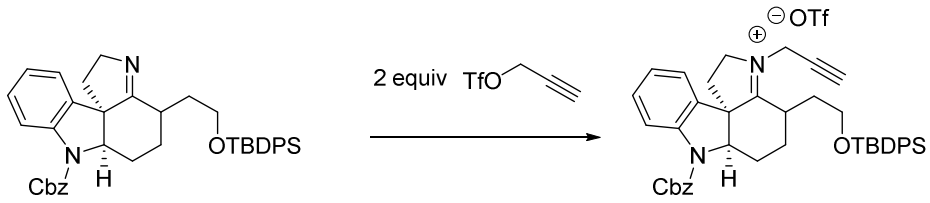


Benzyl (6aR,11bR)-4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1,2,4,5,6,6a-hexahydro-7H-pyrrolo[2,3-d]carbazole-7-carboxylate (3.71-Si)

To a solution of **3.70-Si** (36.7 mg, 0.057 mmol) and potassium azodicarboxylate (1.1391 g, 5.85 mmol) in DCM (5.8 mL, 0.01 M) was added AcOH-DCM mixture (1.97 mL, 1:2) using syringe-pump for 20 h. After completion of syringe-pump addition, the mixture was further stirred for another 3 hours. The reaction mixture was poured into water, and the aqueous phase was extracted with DCM three times. Combined organic layers were dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo*. Flash column chromatography on SiO_2 afforded **3.71-Si** (33.8 mg, 92%).

Partial Characterization of 3.71-Si

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 4H), 7.48 – 7.25 (m, 11H), 6.99 – 6.89 (m, 1H), 6.79 (d, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 7.4 Hz, 0.23H, ***minor diastereomer***), 5.27 (dd, *J* = 27.4, 12.6 Hz, 2H), 4.35 – 4.16 (m, 1H), 4.01 – 3.81 (m, 2H), 3.81 – 3.65 (m, 2H), 2.45 – 2.27 (m, 2H), 2.00 (dd, *J* = 19.3, 15.7 Hz, 2H), 1.87 – 1.49 (m, 3H), 1.40 – 1.18 (m, 2H), 1.14 – 0.82 (m, 9H).



3.71-Si **3.72-Si**

To a solution of **3.71-Si** (3.1 mg, 0.005 mmol) in DCM (0.1 mL, 0.01 M) was added a solution of propargyl triflate (0.01 mL, 1.0 M in CCl_4, 0.01 mmol)[4] at 0 °C under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was thoroughly evaporated under reduce pressure giving a crude **3.72-Si** existing in an equilibrium with **3.73-Si**. Short-lived enamine **3.73-Si** could be obtained by passing through a short pad of silica, and characteristic proton peaks of the propargylic position were observed at δ 4.39 (d, *J* = 18.2 Hz, 1H) and 4.24 (d, *J* = 20.2 Hz, 1H) immediately after evaporation.

Partial Characterization of 3.72-Si — ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.58 (d, *J* = 6.7 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.47 – 7.26 (m, 12H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.81 (br s, 1H), 5.32 (d, *J* = 12.0 Hz, 1H), 5.20 (br s, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 4.93 (d, *J* = 17.4 Hz, 1H), 4.61 – 4.44 (m, 2H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.48 (d, *J* = 6.9 Hz, 2H), 3.01 – 2.78 (m, 2H), 2.67 (s, 1H), 2.54 – 1.72 (m, 7H), 1.04 (s, 9H).

3.5.3. References

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(4) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3673-3677.

국문 초록

본 학위논문은 전이금속 비닐리덴 착물 촉매반응의 개발 및 응용에 대한 연구를 기술한다. 특유의 반응 기작을 지니는 금속 비닐리덴 화합물의 산화적 기능화에 대한 소개에 이어 (제 1 장), 말단 알카인과 이민의 [2 + 2] 고리첨가반응에 대해 논의한다. 후속 연구를 통하여 말단알카인의 산화적 기능화 반응은 사용되는 금속 촉매와 산화제에 따라 다양한 양상을 보일 수 있음을 밝혀내었다 (제 2 장).

새로운 촉매 반응의 개발과 함께, 금속 비닐리덴 반응을 활용한 전합성 연구가 진행되었다. 금속 비닐리덴의 안티-마르코브니코브 선택성을 이용하는 연쇄 고리화 접근법을 고안하여, (+)-펜들러리딘의 전합성 연구를 진행하였다. 제 3 장에서는 (+)-펜들러리딘의 최초 거울상선택적 합성을 위한 연구를 소개하였다.

주요어: 금속 비닐리덴, 산화적 기능화, 촉매 반응, 전합성, (+)−펜들러리딘

학번: 2014 - 31008

감사의 글

스물세 살 때 처음으로 연구실의 문을 두드린 후 이제 십 년이 지났습니다. 십 년이라는 시간이 흐르는 동안 강산이 변하기는 하는건지 실감이 안 납니다만, 사람이 변한다는 것은 알 수 있었습니다. 대학원 시절을 돌이켜 보니 고마운 분들과 함께한 소중한 시간들이 있었기에 지금의 제가 있는 것 같습니다.

가장 먼저 학사, 석사, 그리고 박사과정까지 저의 모든 학위를 지도해 주신 이철범 교수님께 무한한 감사를 전하고 싶습니다. 선생님께 물려받은 것들이 너무나 많습니다. 유기화학 지식에 더하여, 생각을 글로 정리하는 방법, 배움을 청하는 자세, 남을 가르칠 때의 마음가짐, 그리고 세상을 바라보는 눈까지 정말 말로 표현하기 힘들 정도로 많은 것을 제게 알려주셨습니다. 선생님의 지도 덕분에 자만과 나태에 빠지지 않고 계속 정진할 수 있었고, 사회로 나가는 첫 발을 디딜 준비가 되었습니다. 부끄럽지 않은 제자가 될 수 있도록 졸업 후에도 선생님의 가르침들을 항상 기억하겠습니다.

중요한 발표 때 마다 심사위원장을 맡아주신 김병문 교수님, 항상 따듯한 격려를 해주셨던 홍종인 교수님, 매번 날카로운 지적과 조언을 해주셨던 이홍근 교수님, 그리고 청암 펠로우쉽 때부터 저의 학위과정을 진심으로 응원해 주신 유은정 교수님, 네 분 심사위원님께 깊은 감사의 말씀을 드립니다.

연구실에서 만난 소중한 사람들이 있습니다. 사수로써, 그리고 너무나도 압도적인 실력으로 저의 목표가 되어 주셨던 재훈이형, 같이 생활했던 시간은 짧았지만 이후에도 많은 조언을 해주셨던 기포형, 상국이형, 그리고 민상이형, 좌충우돌 난장판을 만들고 있을 때마다 먼저 다가와 가르침을 주었던 혜진누나, 지현누나, 현정누나, 그리고 명수형께

감사드립니다. 어렸을 때부터 함께 절차탁마 해왔던 희준이, 성실하고 누구보다도 어른스러웠던 성환이, 마찬가지로 제가 형이라는 소리를 듣기가 민망할 정도로 현명했던 태교, 이 세 사람의 영향을 받은 덕분에 학부의 마지막과 연구실 생활의 시작을 부끄러움 없이 보낼 수 있었습니다.

607 호 애늙은이 막내를 챙기느라 고생 많으셨던 은혜누나, 승주누나에게도 깊은 감사의 말씀을 드립니다. 연구실에서처럼 직장에서도 사람들을 이어주는 중심이 되어 있으시겠죠. 고집불통이었던 저에게 솔직한 조언을 건네고 진지한 토론을 꺼리지 않았던 사람들에게 감사합니다. 호윤이와 성현이형 덕분에 서른이 다 될 때까지 치기 어린 행동을 하고 다녔던 제가 많이 바뀔 수 있었습니다.

함께 전합성 분야에서 연구하느라 고생했던 동석이형과 선우형, 친구로써 그리고 동료로써 오랜 시간 같이 했던 진이, 재우, 성미, 본인의 일에 충실했던 후배들 여울이, 수홍이, 호준이, 희경이, 인환이, 중기. 모두 각자의 위치에서 앞으로도 좋은 결과 내리라 믿고 있습니다. 감사합니다.

앞으로 실험실을 이끌어 나갈 지숙이, 현석이, 대권이, 우경이, 혜지, 혜인이, 태현이. 아저씨 개그에도 잘 웃어주고 연구실에서의 말년 시절을 외롭지 않게 만들어 주어 너무나 고맙습니다. 다들 큰 뜻을 품고 있으니 이대로 꾸준히 선생님의 지도를 따라가면 좋은 결과들이 있으리라 믿습니다.

마지막으로 동고동락했던 비닐리덴 팀 멤버들께 진심으로 감사드립니다. 항상 저를 높게 평가해주고 대등하게 연구할 기회를 주었던 인수형, 그리고 이제는 아픔 없는 곳에서 저희를 지켜봐 주고 계실 동길이형, 형들에게 정말 많은 것을 배웠습니다. 감사합니다. 함께 리뷰 쓰느라 고생했고, 묵묵하게 혼자서 실험실의 일꾼 역할을 하는 경민이 덕분에 정신 없었던 학위과정의 후반부를 무사히 헤쳐 나올 수 있었습니다. 고맙다 경민아.

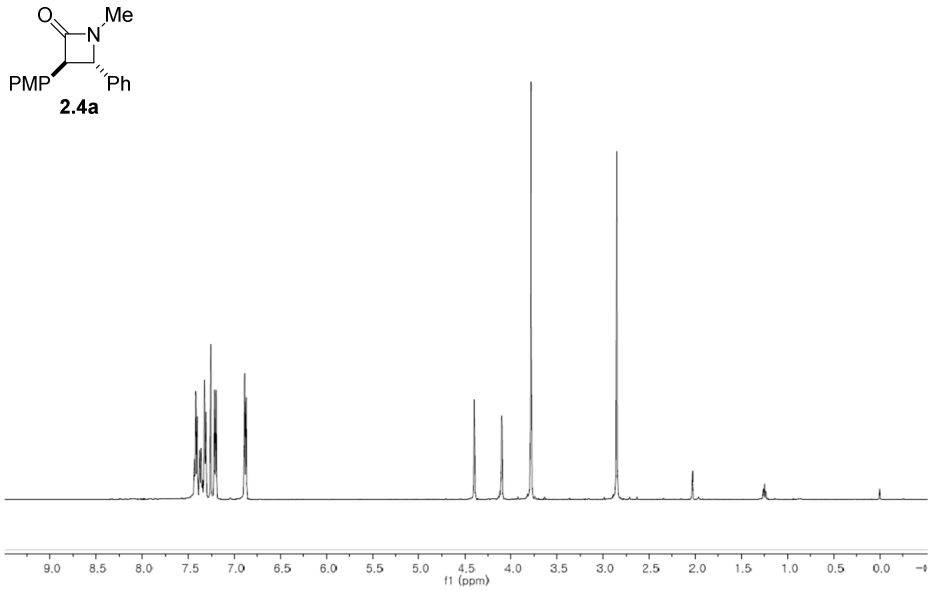
기나긴 학업의 과정 내내 물심양면으로 지원해 준 가족들이 아니었으면 일찌감치 공부를 포기했을 수도 있었다는 생각이 듭니다. 어머니, 누나, 그리고 매형께 감사드립니다. 그리고 아무것도 가진 것 없던 대학원생에게 딸과의 결혼을 허락해 주신 장인어른, 장모님과 물심양면으로 저희 부부를 지원해주신 형님께 감사드립니다.

누구보다도 나를 믿어주고, 누구보다도 큰 힘이 되어준 사랑하는 아내 선민. 나에게 보내주었던 무한한 신뢰 덕분에 힘든 일이 닥쳐와도 스스로를 믿고 헤쳐 나갈 수 있었습니다. 평생 지금처럼만 즐겁게 지내도 무엇과도 바꿀 수 없는 행복이겠지만, 앞으로 우리가 상상도 못 한 더 큰 행복들을 함께할 수 있으리라 믿어 의심치 않습니다. 감사하고 사랑합니다.

2019 년 8 월 학위과정을 마무리하며

노 상 원

Spectra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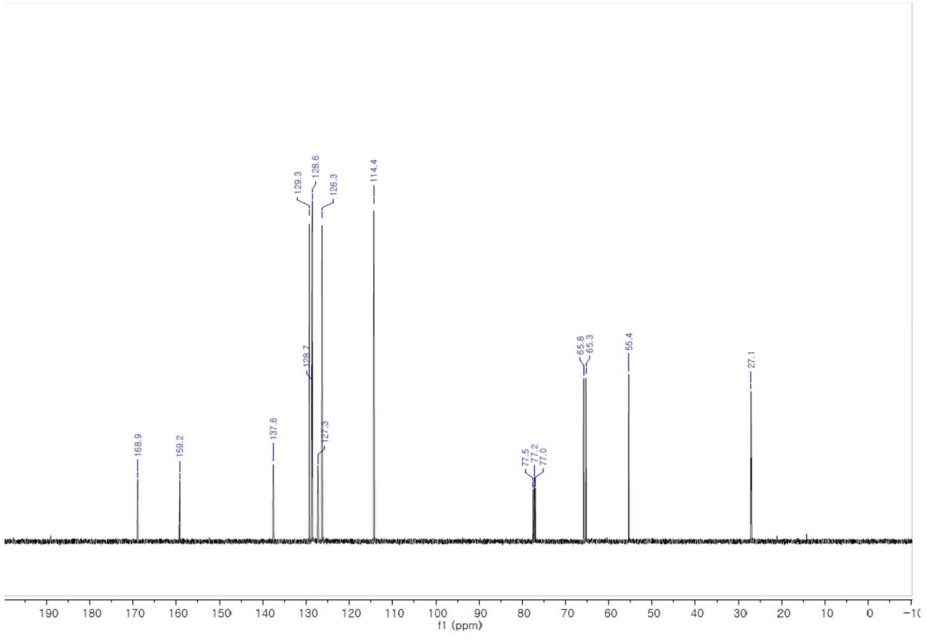
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77.2
77.0
65.8
65.3
55.4
27.1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
Me
n-Bu
Ph

2.4b

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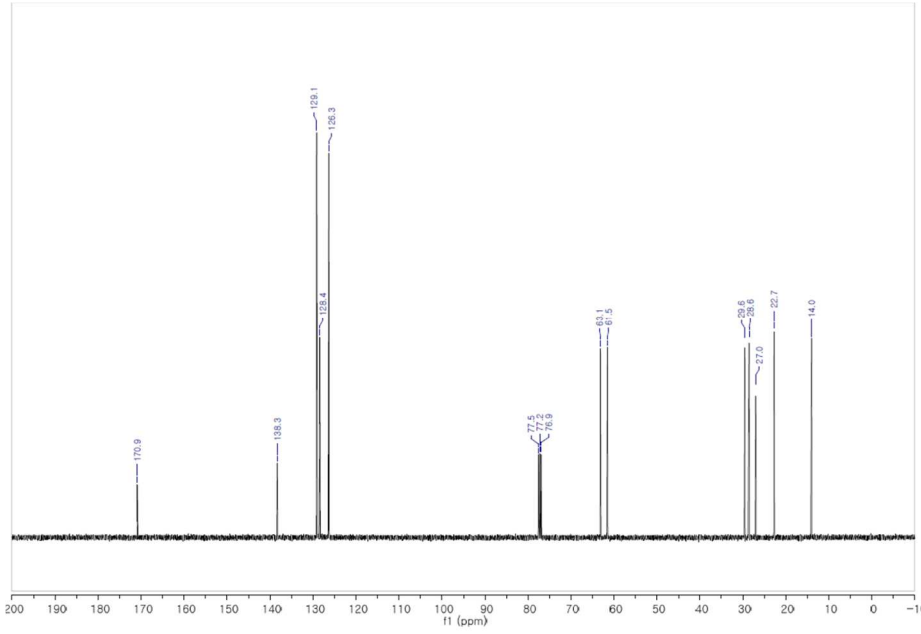
1.01
1.06
3.00
1.24
1.28
2.27
2.41
3.19
f1 (ppm)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28.6
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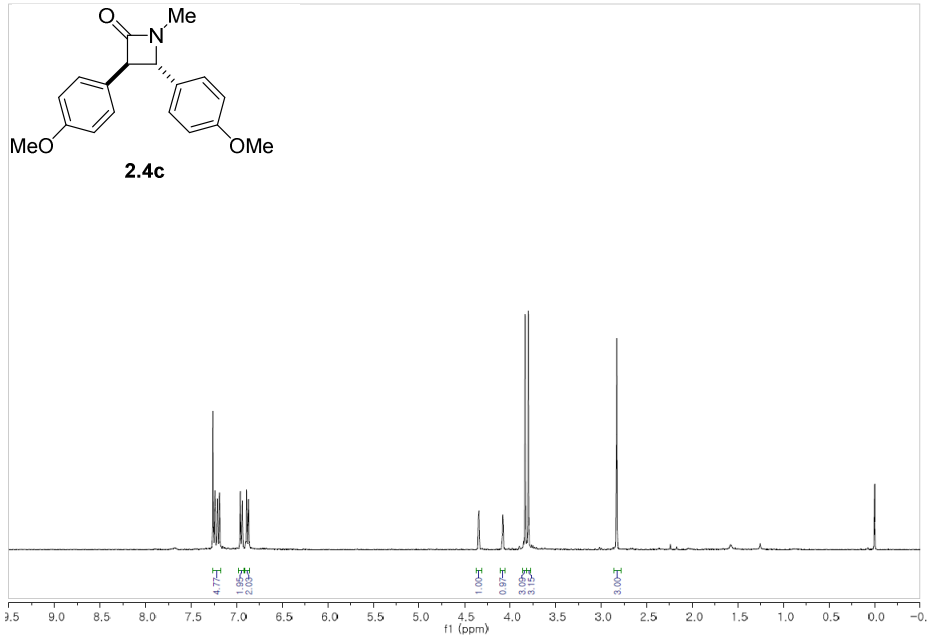
14.0
f1 (ppm)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Me
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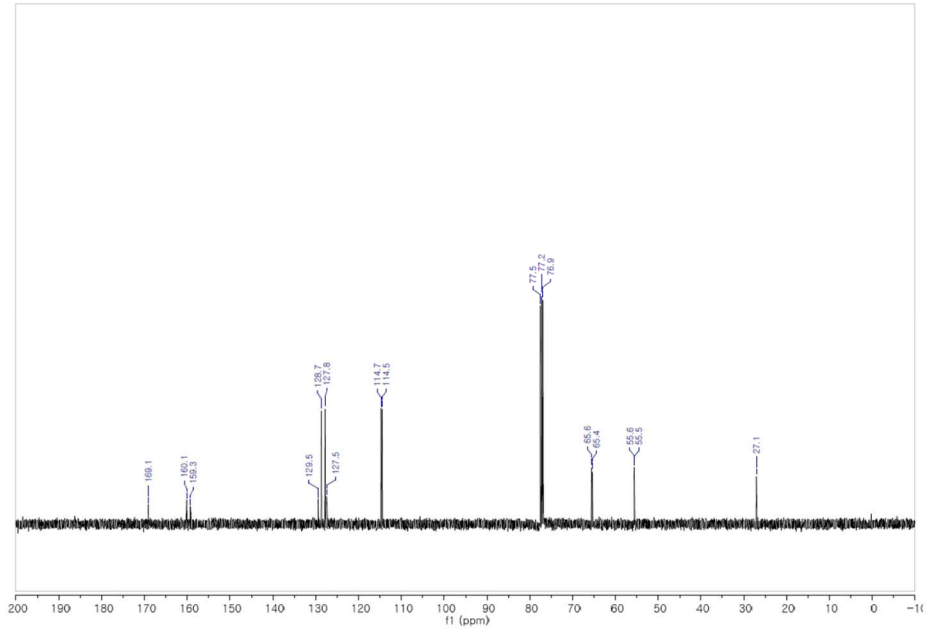
3.15
3.00
f1 (ppm)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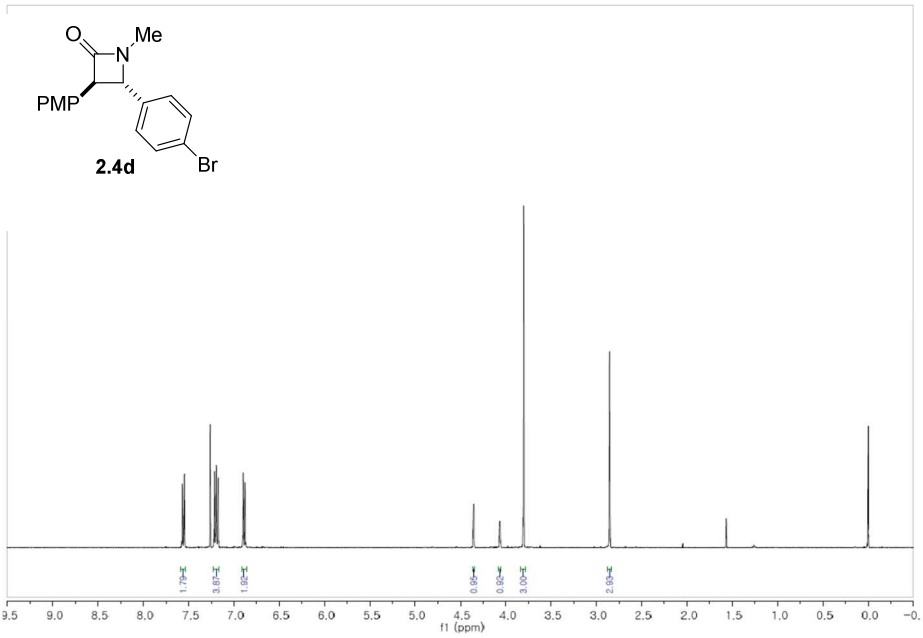
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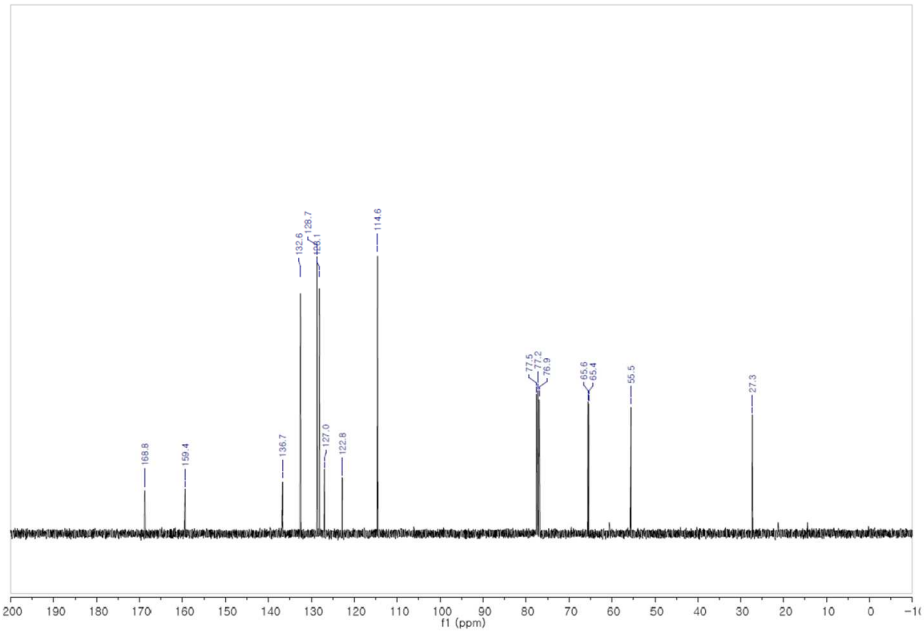
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27.3
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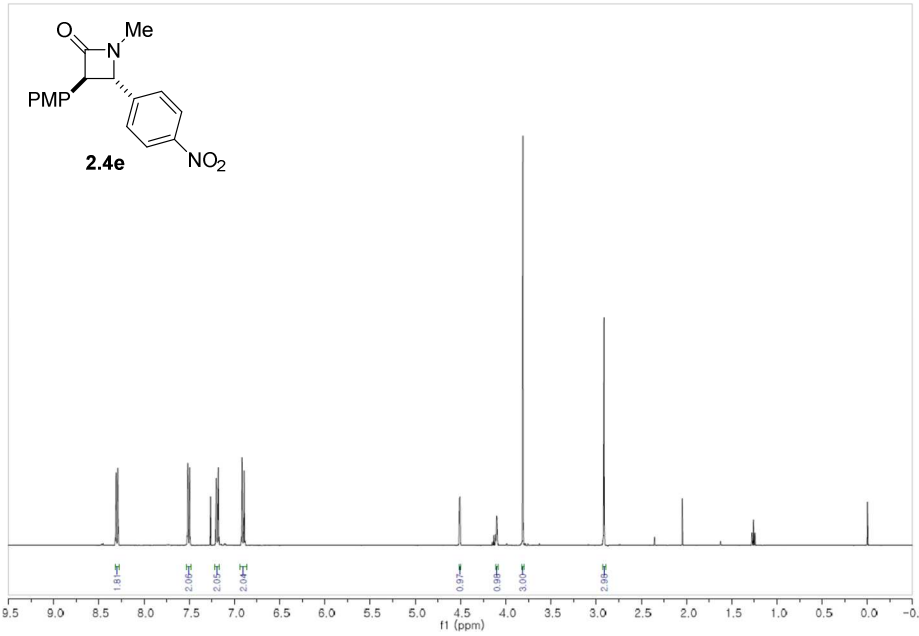
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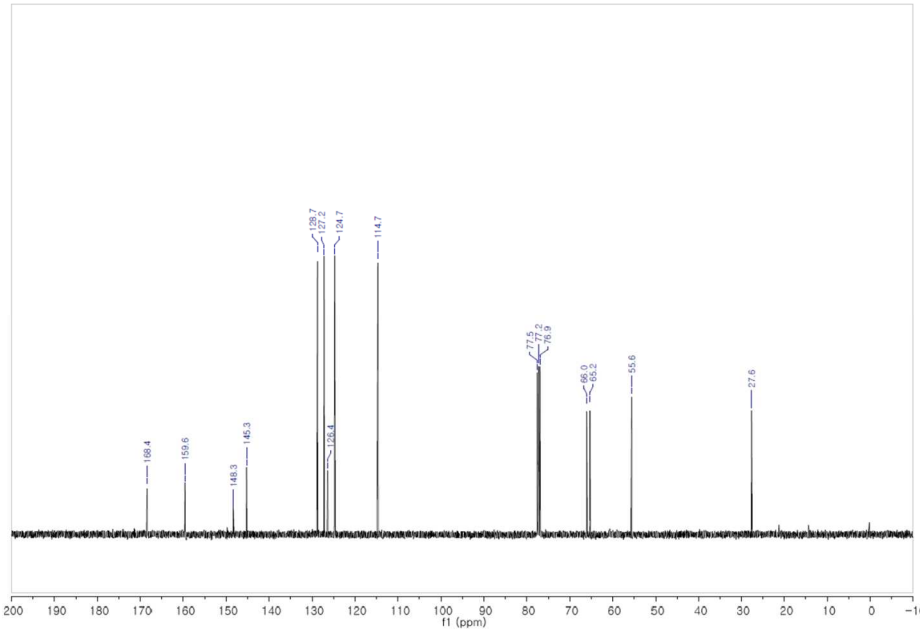
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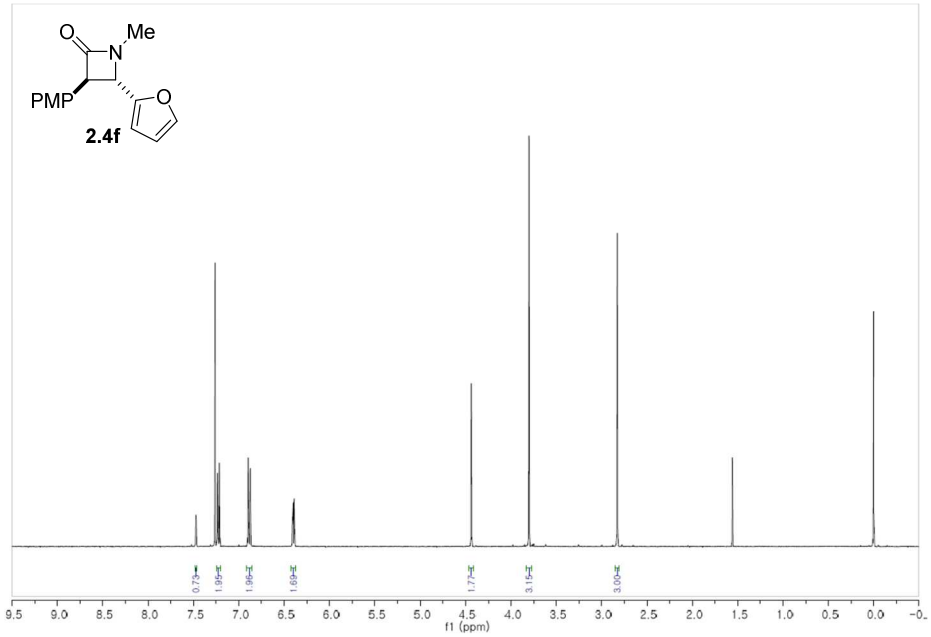
55.6
27.6
f1 (ppm)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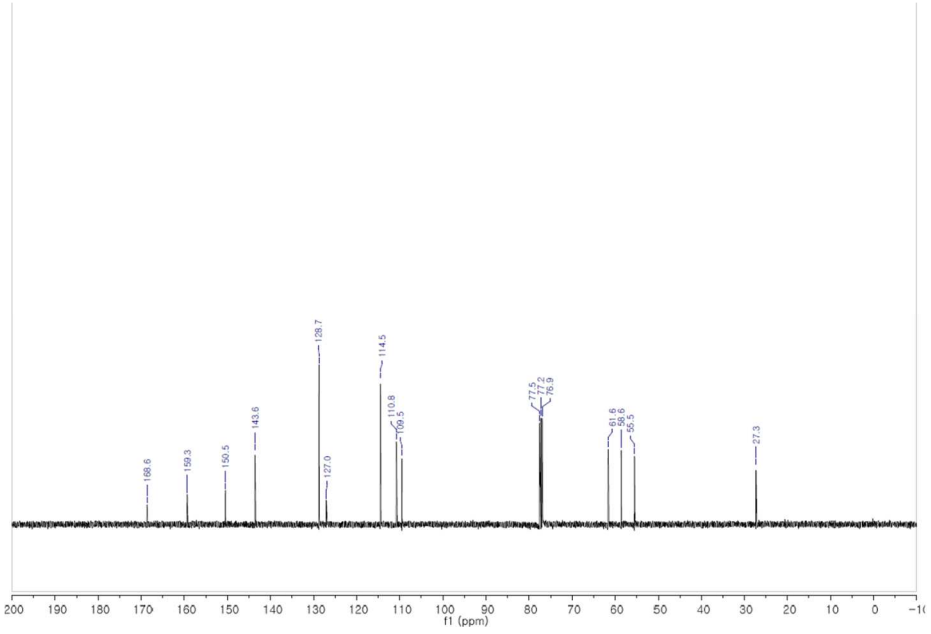
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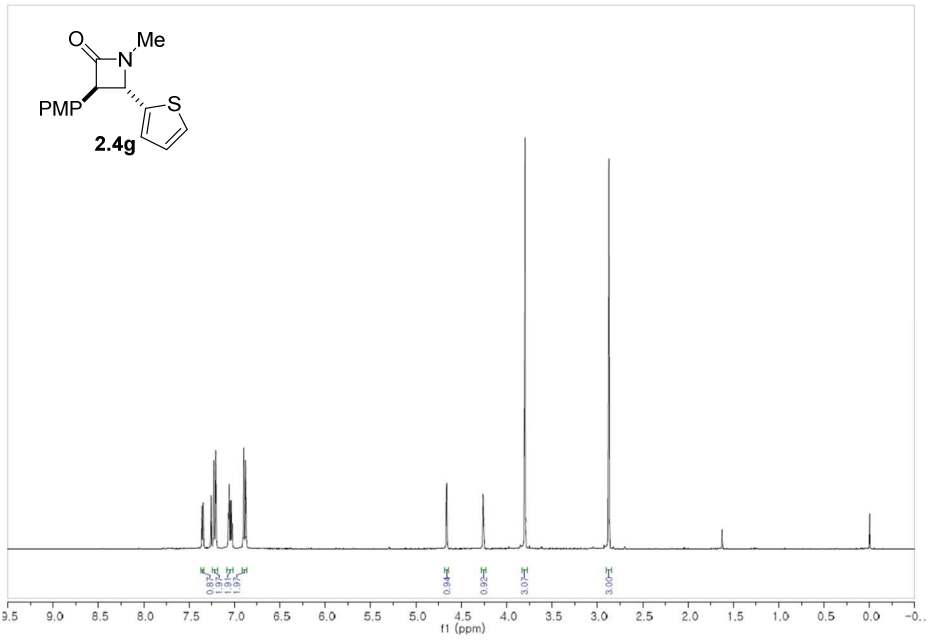
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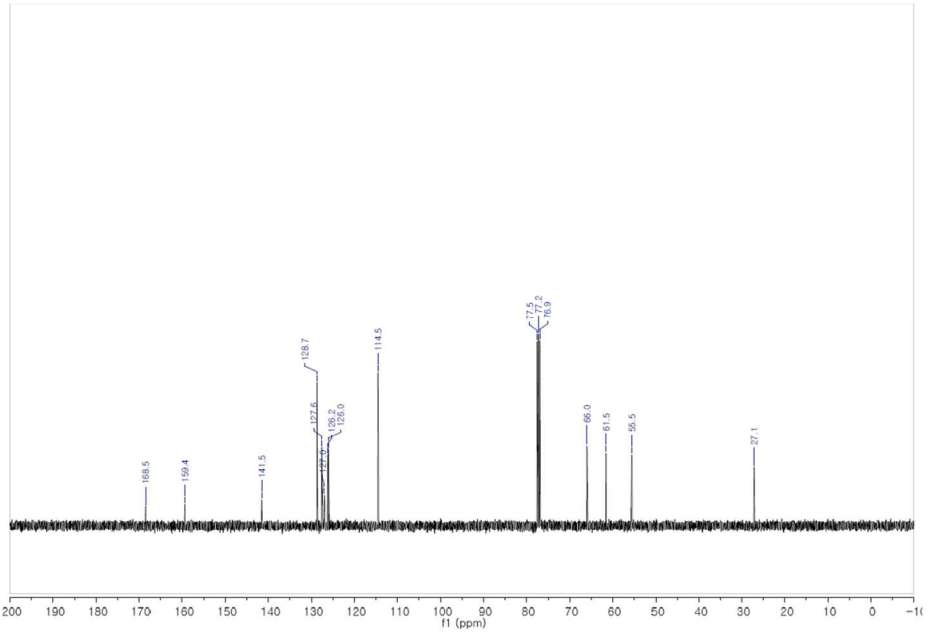
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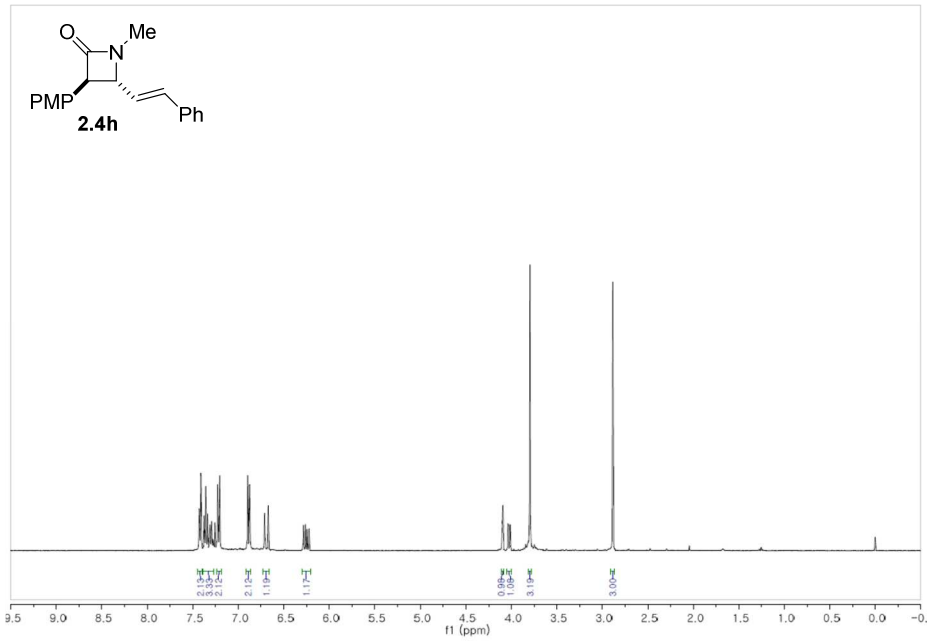
27.1
f1 (ppm)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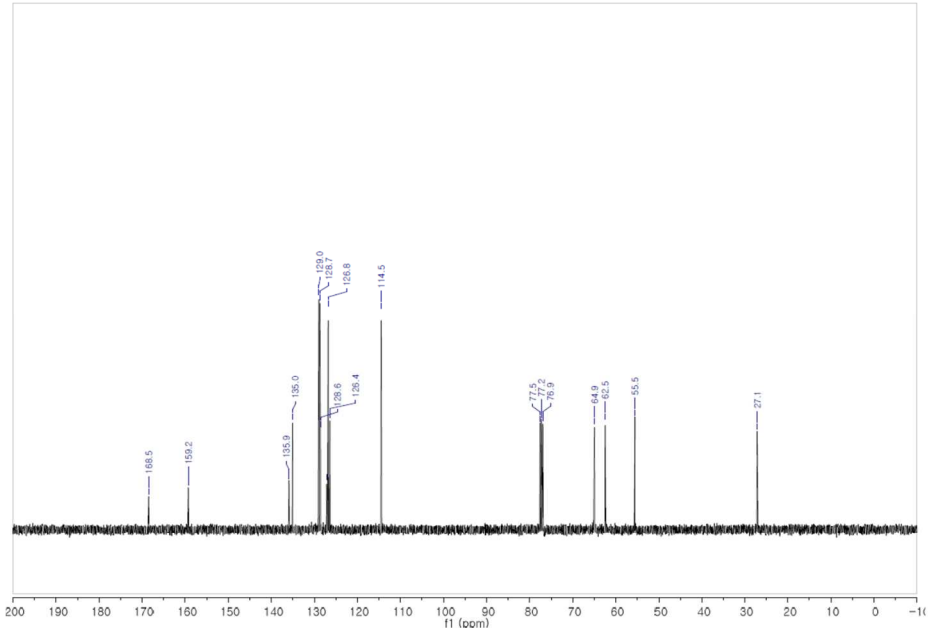
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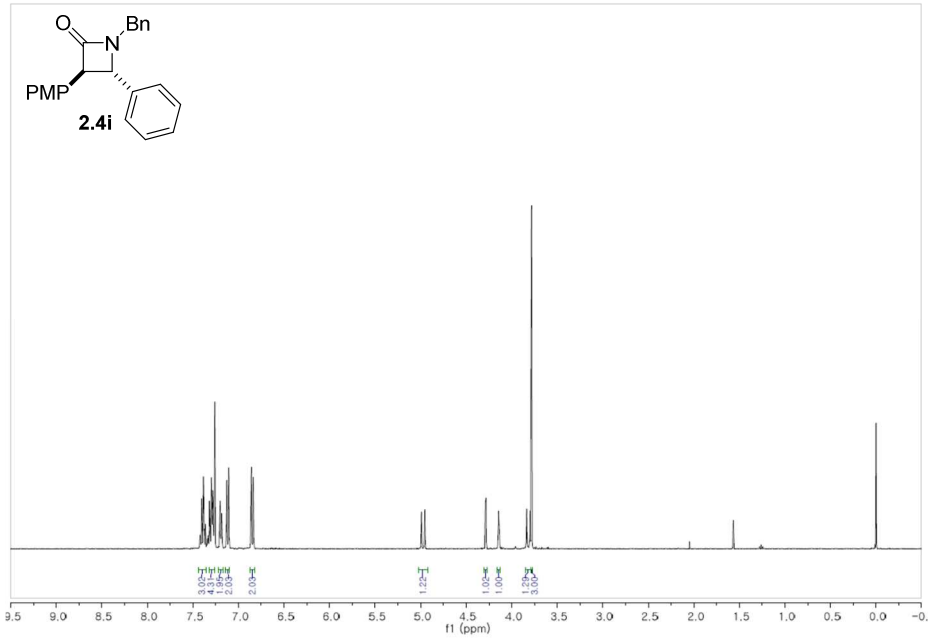
27.1
f1 (ppm)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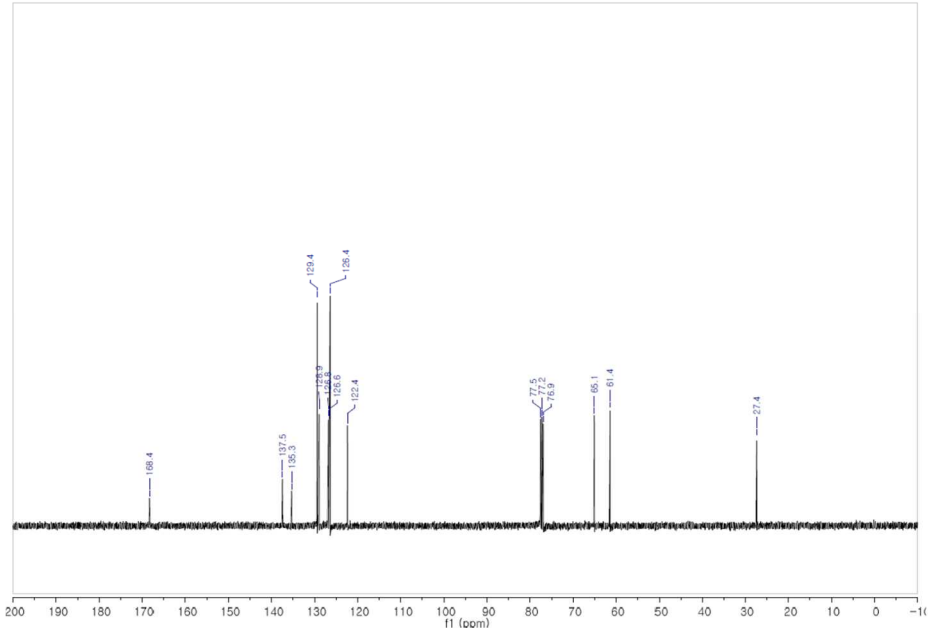
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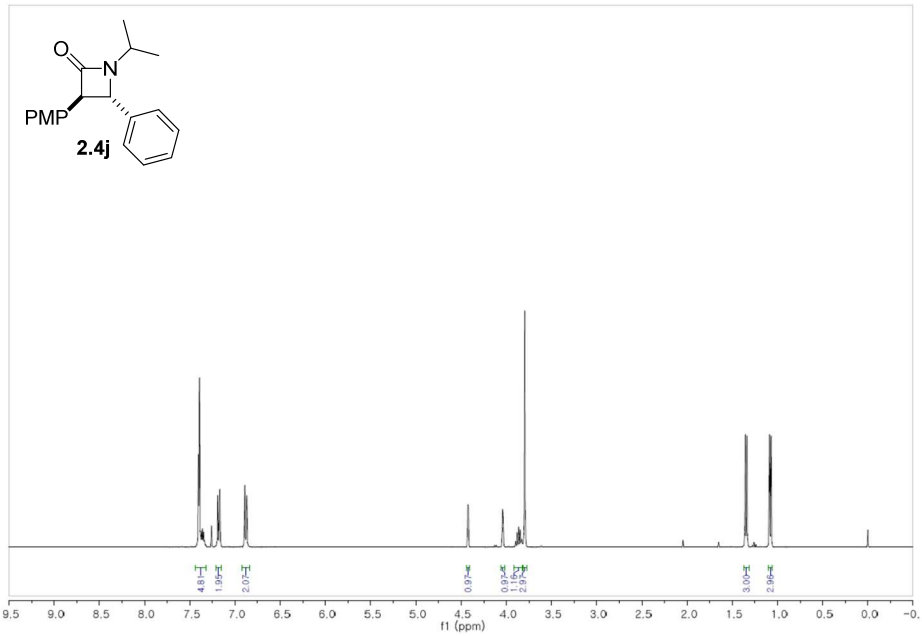
f1 (ppm)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N
PMP
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2.07
0.97
0.93
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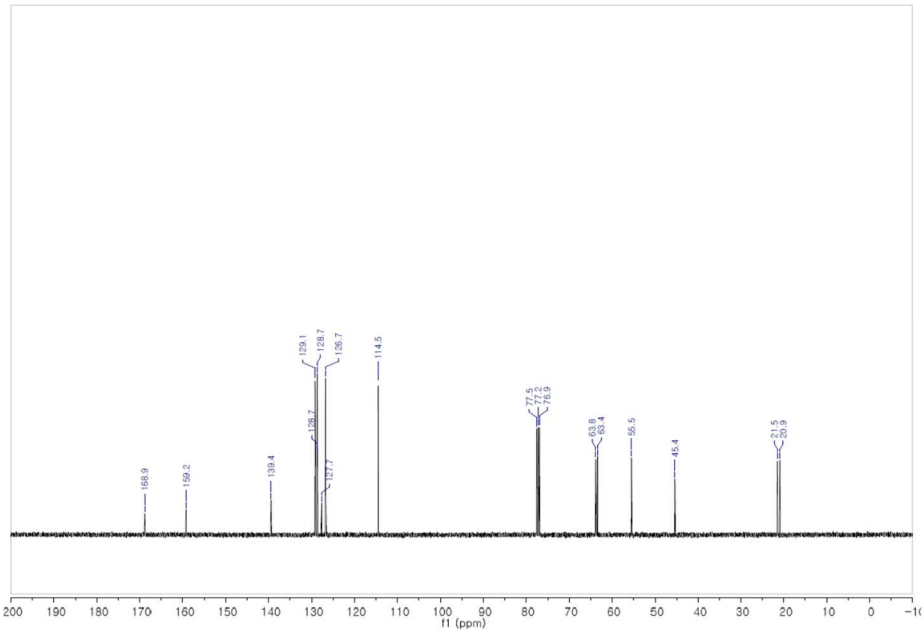
2.91
3.00
2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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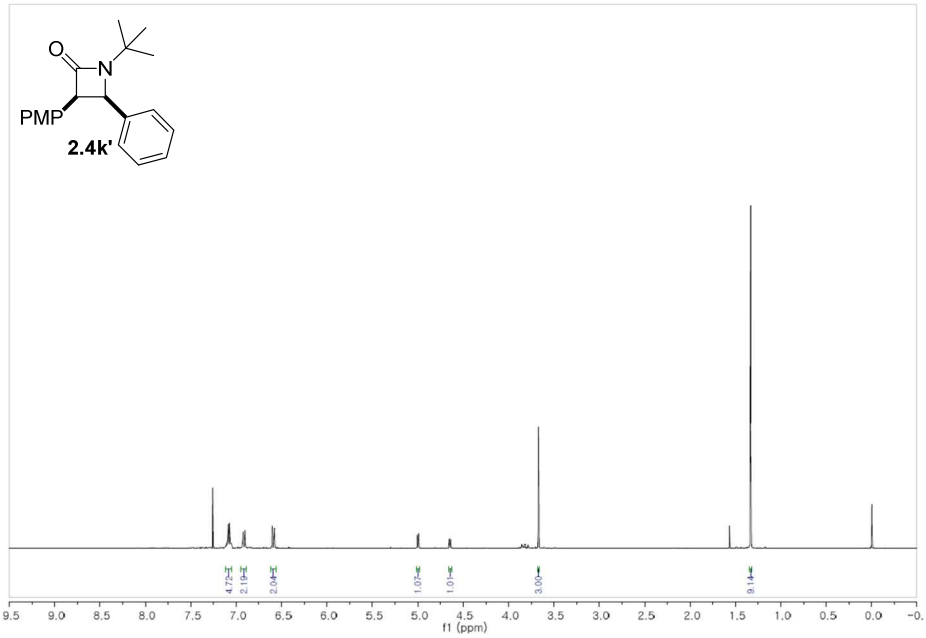
159.2
139.4
129.1
128.7
126.7
127.7
135.7
114.5
77.5
77.2
76.9
63.8
63.4
55.5
45.4
21.5
20.8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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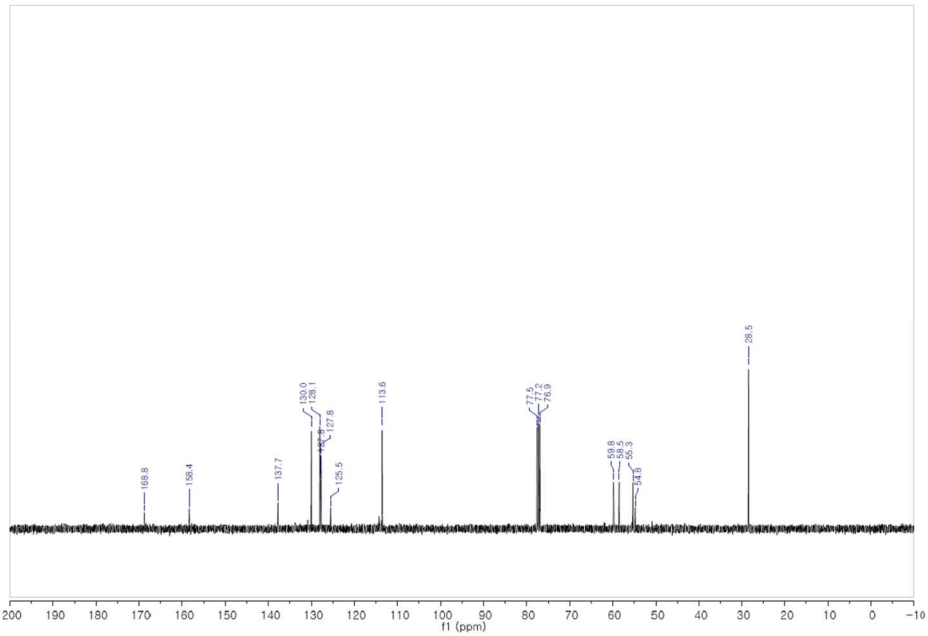
1.01
3.00
9.14
f1 (ppm)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128.1
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113.6
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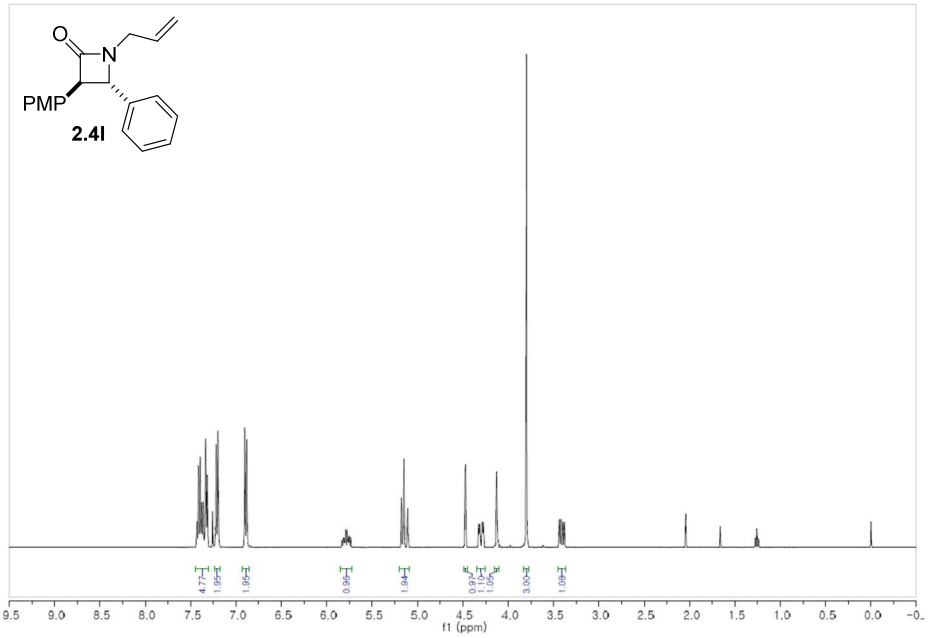
77.2
76.9
59.8
58.5
55.3
34.6
28.5
f1 (ppm)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PMP
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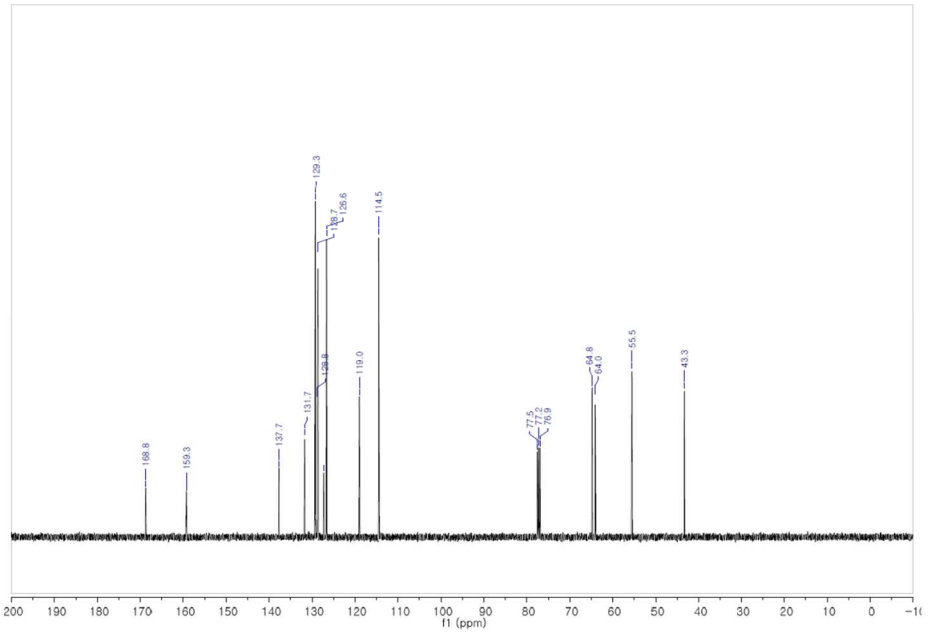
1.94
0.97
1.15
1.05
3.00
1.08
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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137.7
131.7
129.3
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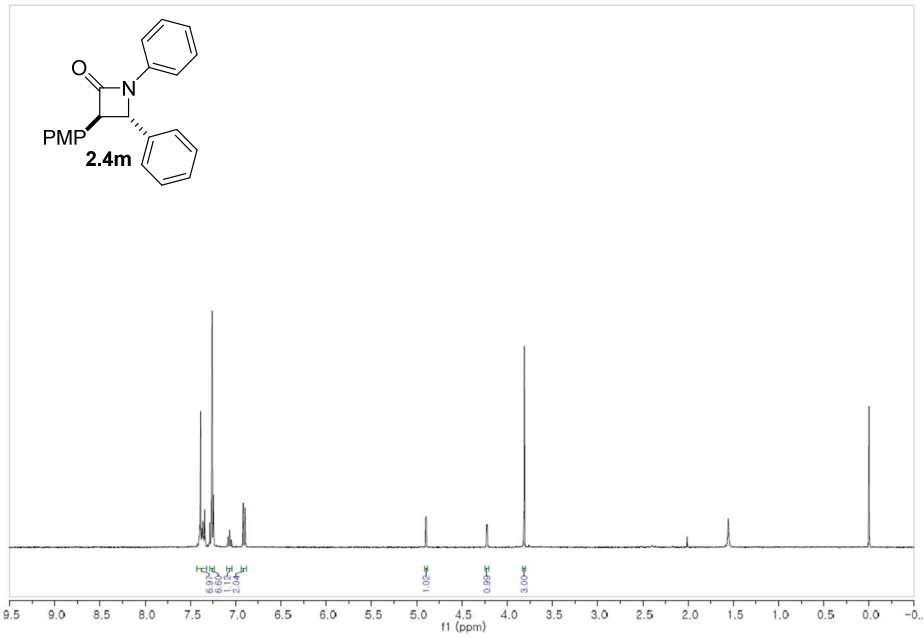
128.6
119.0
114.5
77.5
77.2
76.9
64.8
64.0
55.5
43.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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PMP
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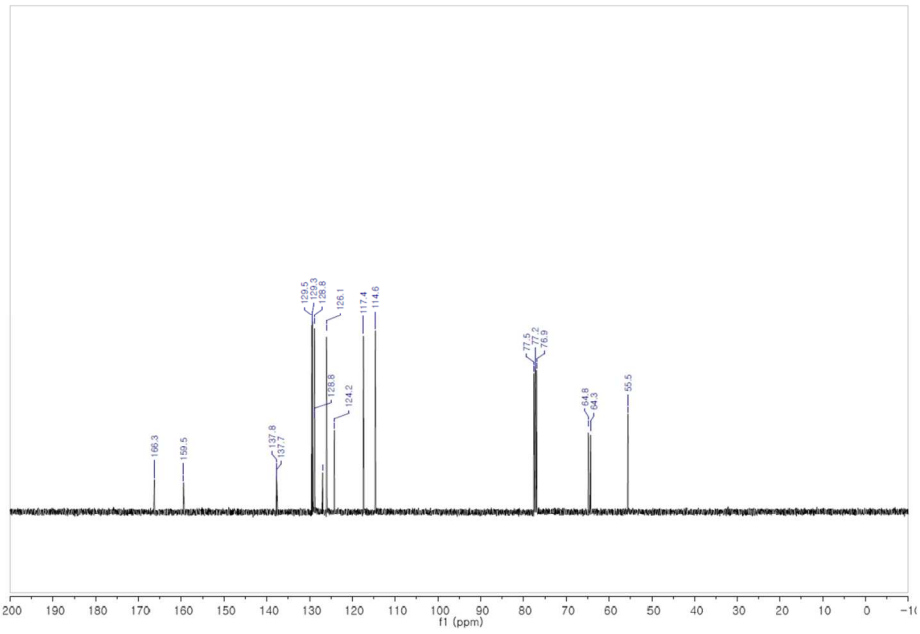
2.06
1.00
0.99
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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137.7
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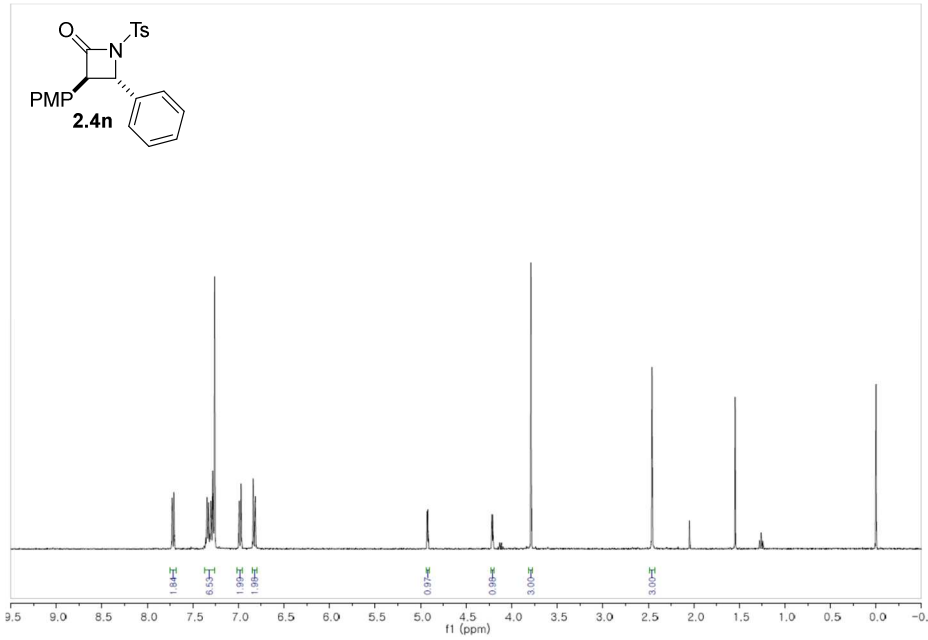
129.3
128.8
126.1
128.8
124.2
117.4
114.6
77.5
77.2
76.9
64.8
64.3
55.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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N
Ts
PMP
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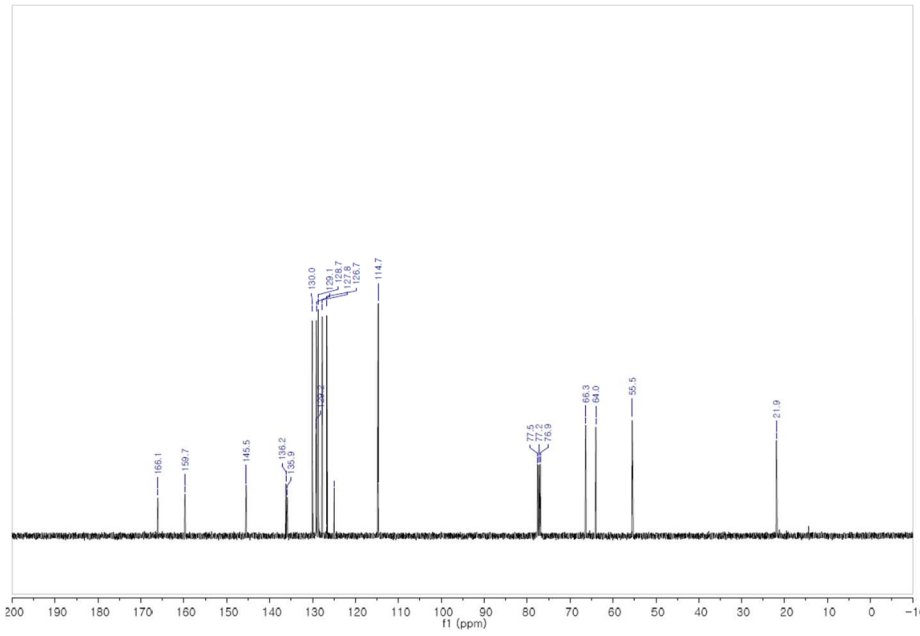
1.98
0.97
0.98
3.00
3.00
f1 (ppm)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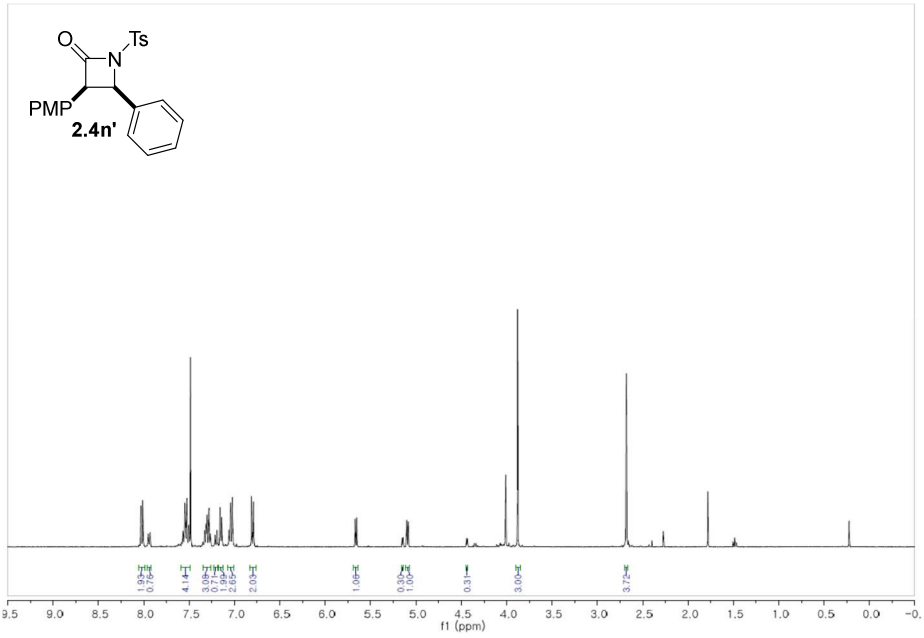
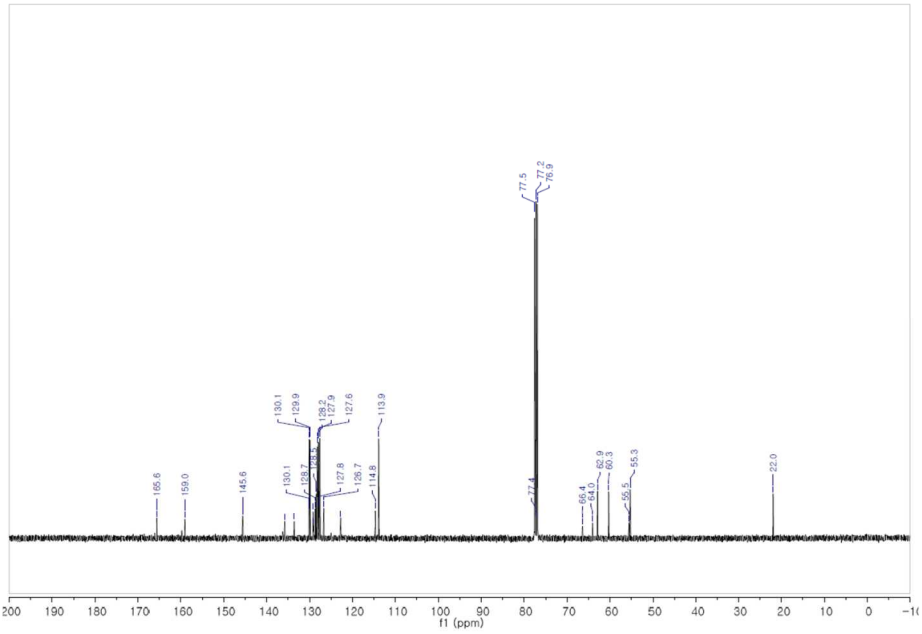
159.7
145.5
136.2
135.9
130.0
129.1
128.7
127.8
126.7
114.7
77.5
77.2
76.9
66.3
64.0
55.5
21.9
f1 (ppm)


O
Ts
N
PMP
2.4n'
f1 (ppm)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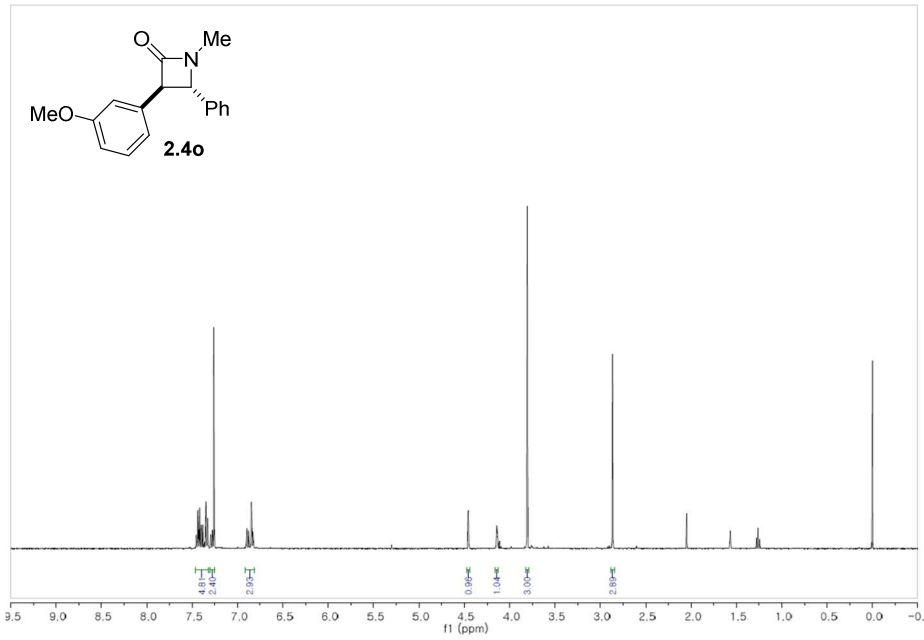
77.2
76.9
130.1
129.9
128.7
127.9
127.6
113.9
127.8
126.7
114.8
185.6
159.0
145.6
77.4
66.4
64.0
62.9
60.3
55.5
55.3
22.0
f1 (ppm)


O
N
Me
Ph
MeO
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2.40
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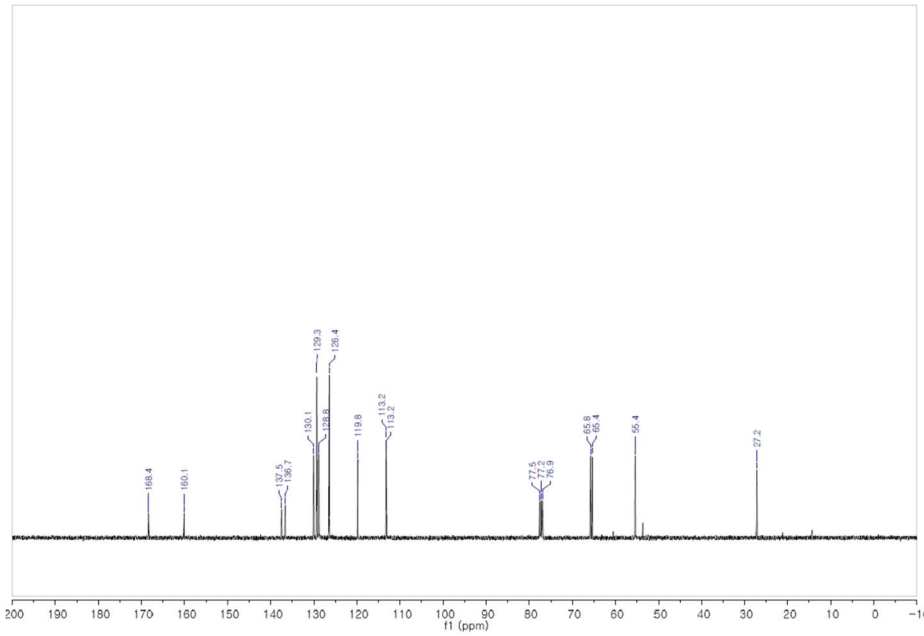
0.96
1.04
3.00
2.80
f1 (ppm)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130.1
129.3
128.8
126.4
119.8
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113.2
77.5
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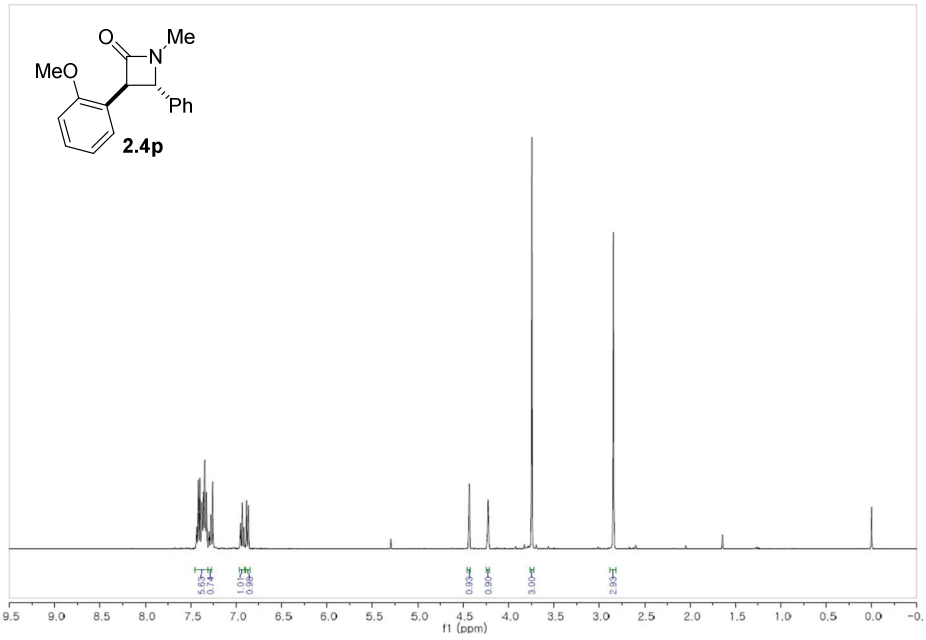
65.8
65.4
55.4
27.2
f1 (ppm)


O
N
Me
MeO
Ph
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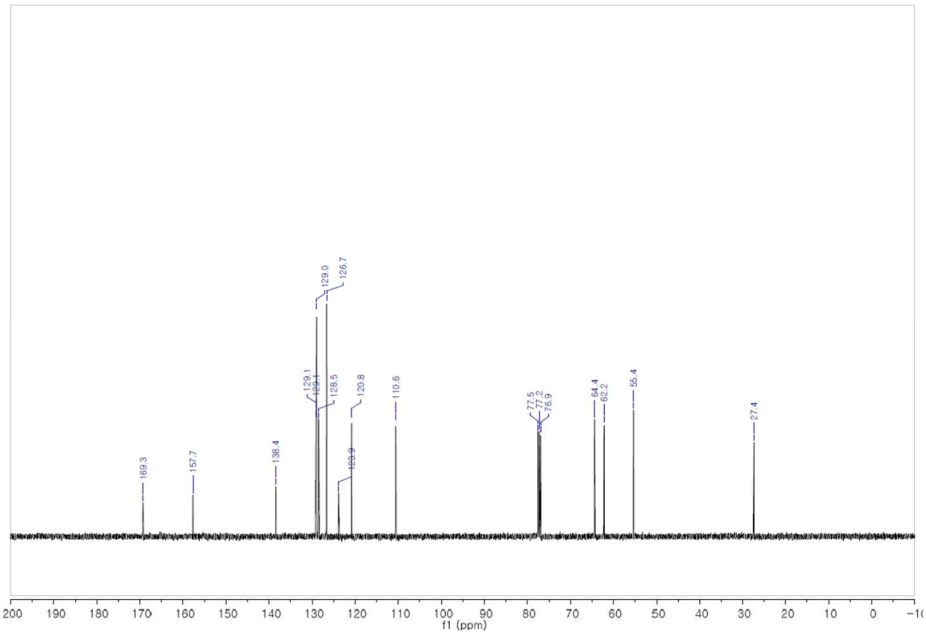
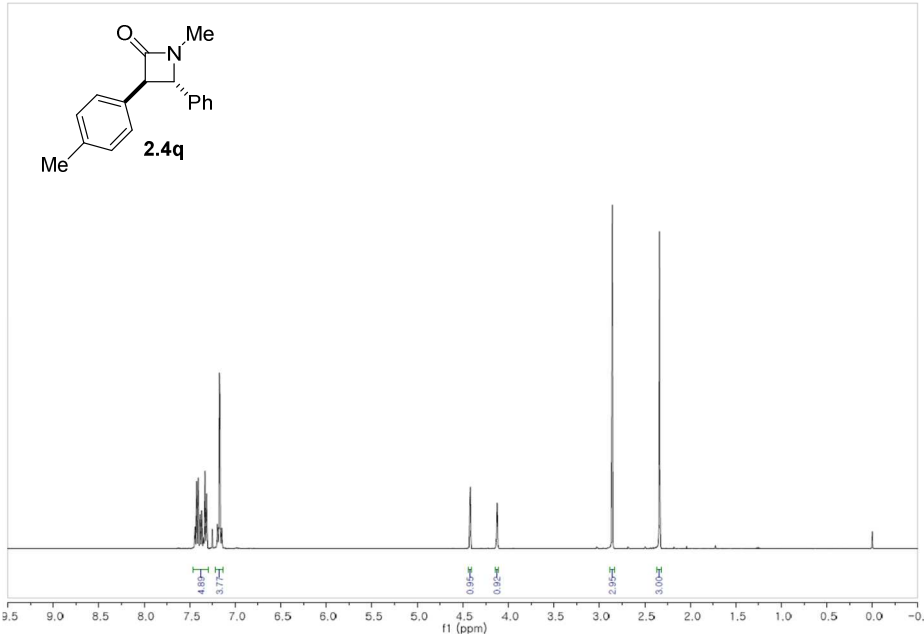
0.88
0.93
0.90
3.00
2.89
f1 (ppm)


169.3
157.7
138.4
129.1
129.0
128.5
126.7
120.8
110.6
77.5
77.2
76.9
64.4
62.2
55.4
27.4
f1 (ppm)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N
Me
Ph
Me
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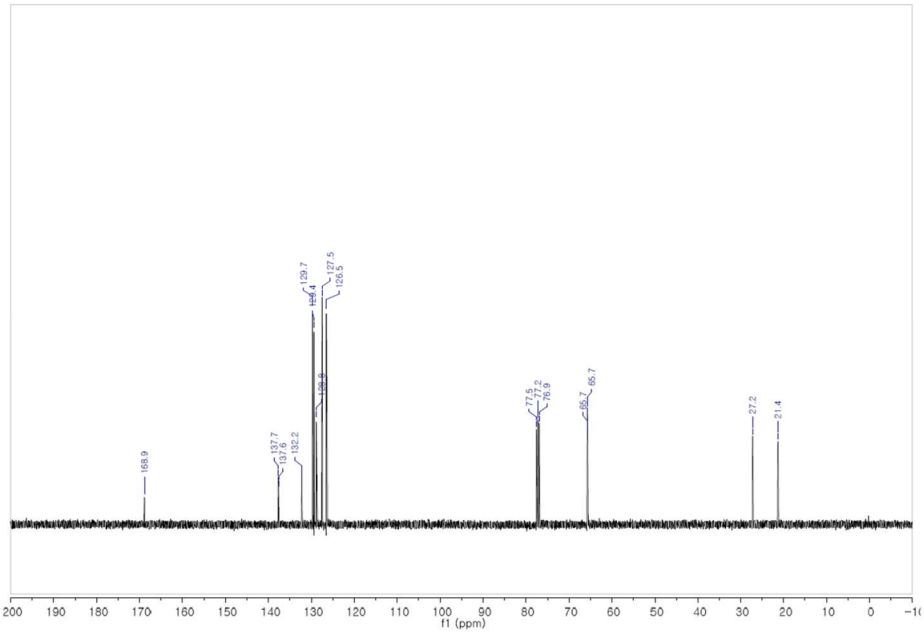
3.77
0.95
0.92
2.94
3.00
f1 (ppm)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132.2
129.7
129.4
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128.3
127.5
126.5
77.5
77.2
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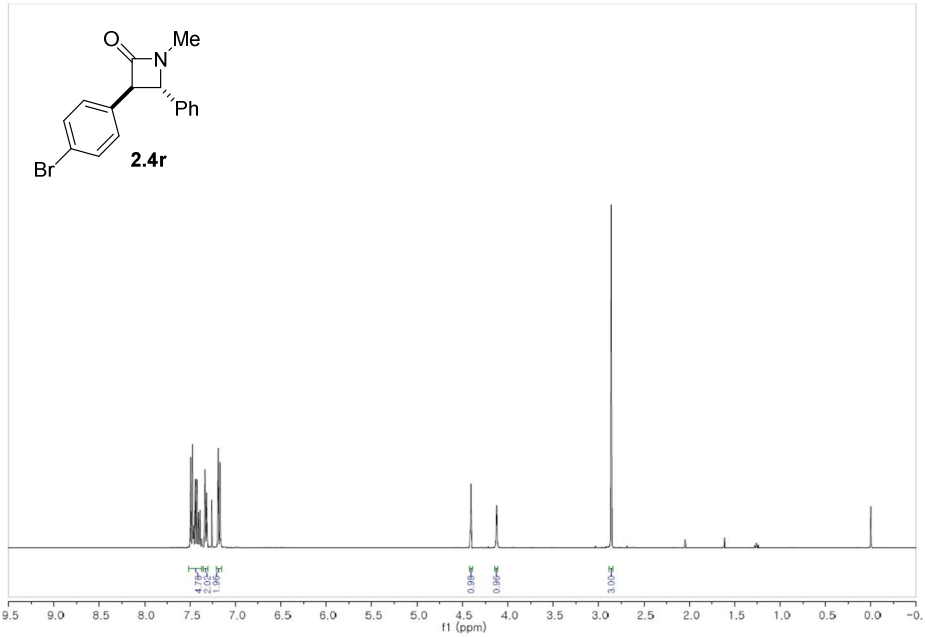
65.7
65.7
27.2
21.4
f1 (ppm)


O
N
Me
Ph
Br
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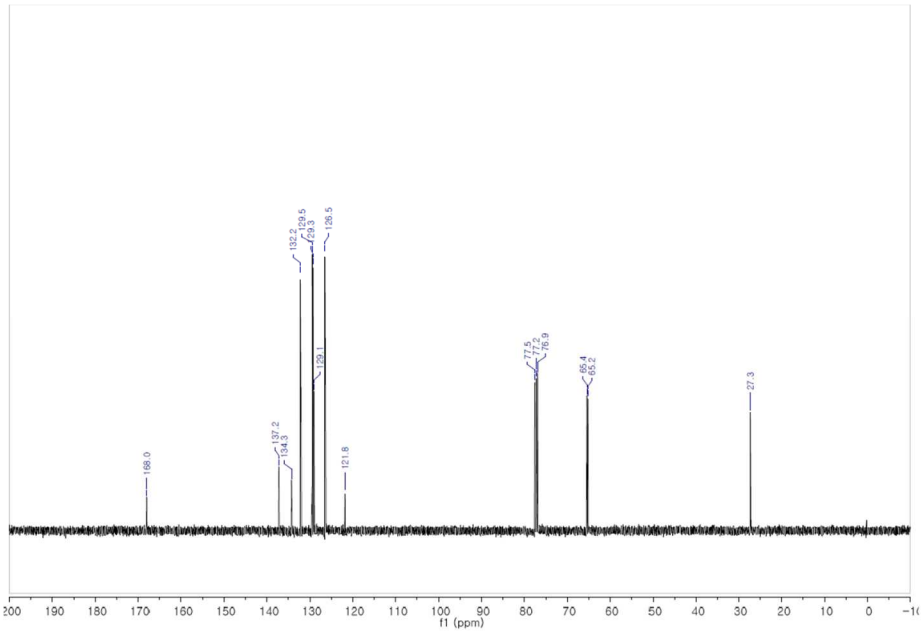
4.07
4.04
1.96
0.98
0.96
3.00
f1 (ppm)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134.3
132.2
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129.3
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77.5
77.2
76.8
65.4
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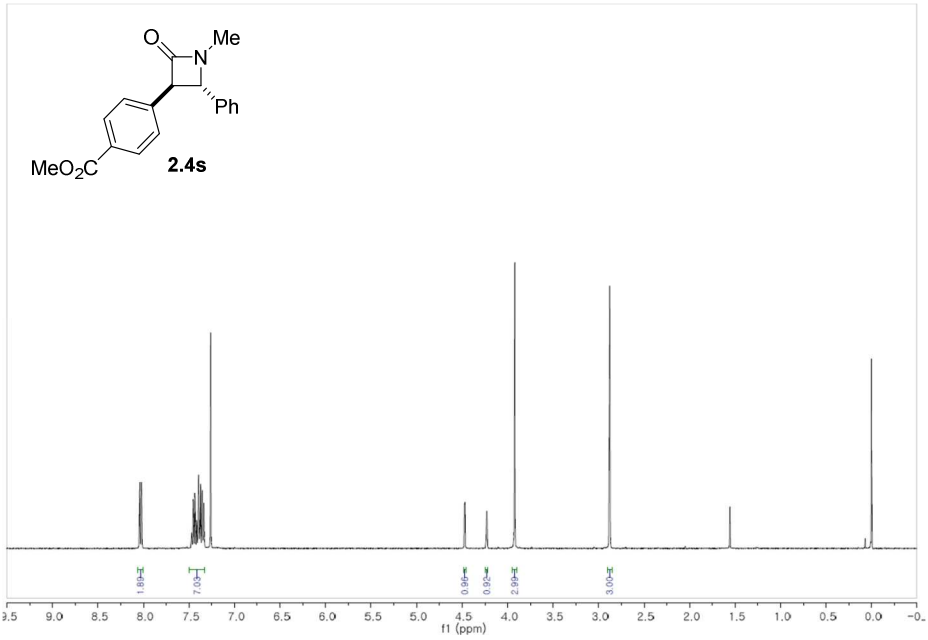
27.3
f1 (ppm)


O
N
Me
Ph
MeO2C
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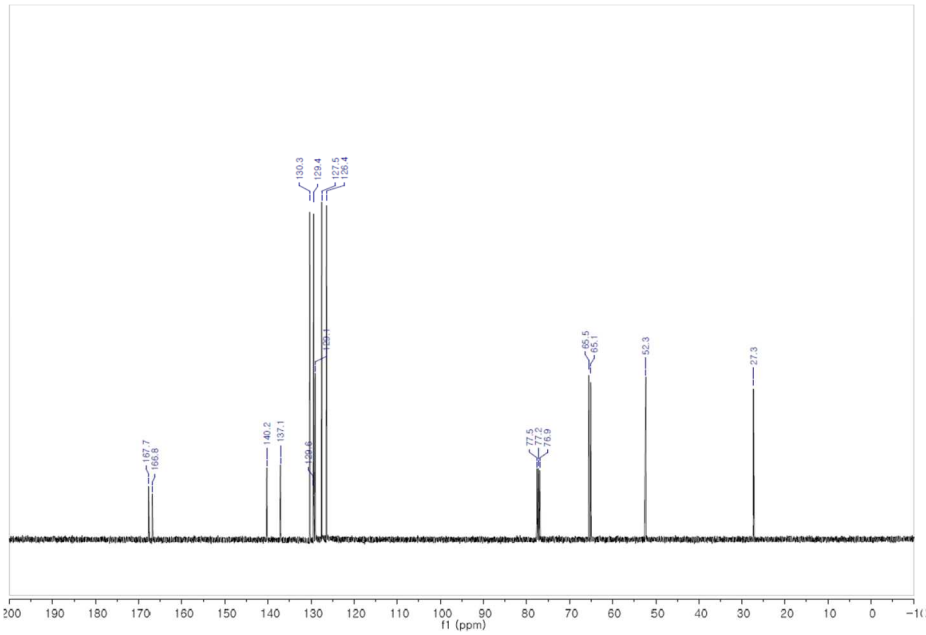
1.89
7.09
0.96
0.93
2.99
3.00
f1 (ppm)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166.8
140.2
137.1
130.3
129.4
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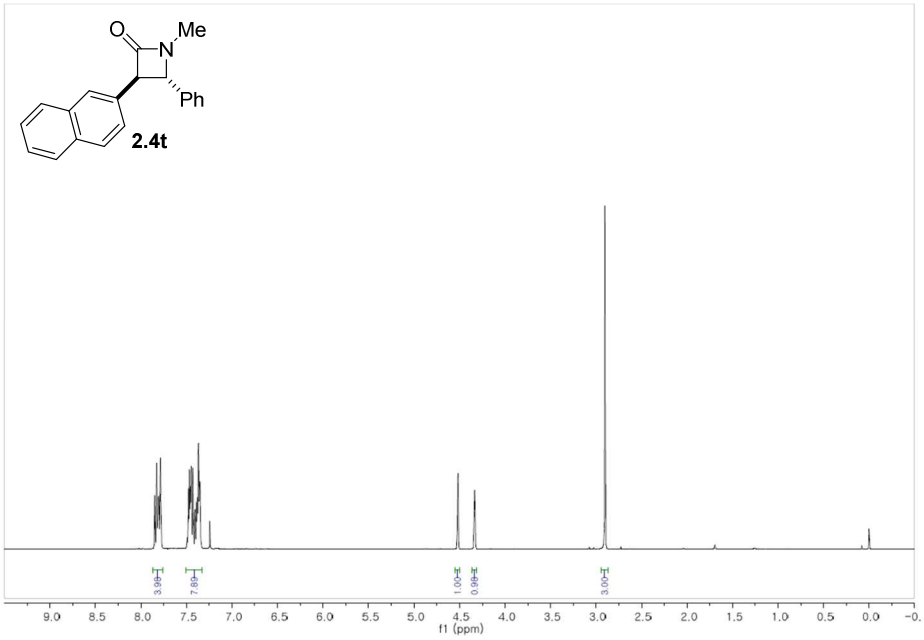
126.4
77.5
77.2
76.9
65.5
65.1
52.3
27.3
f1 (ppm)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N
Me
Ph
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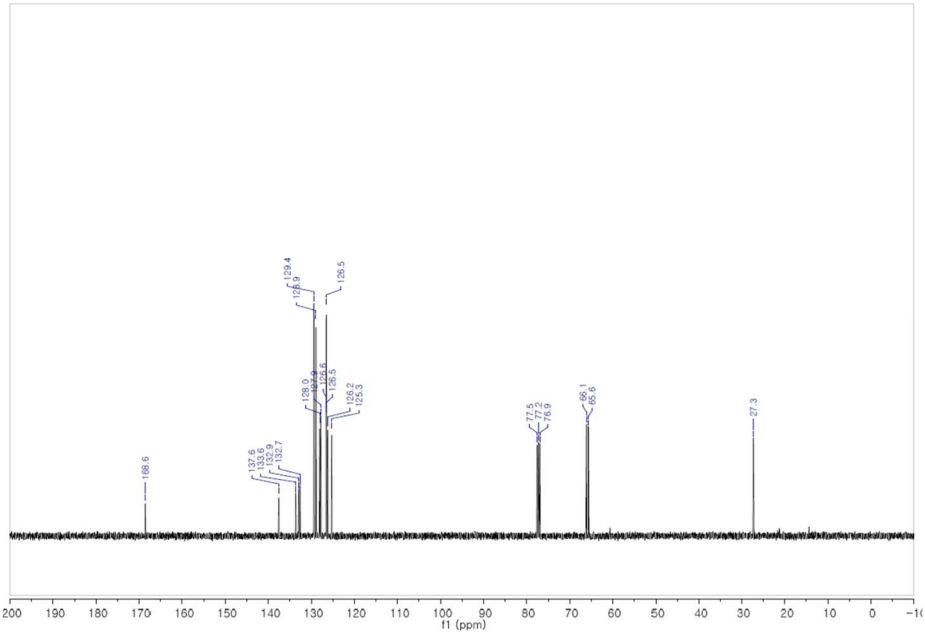
0.98
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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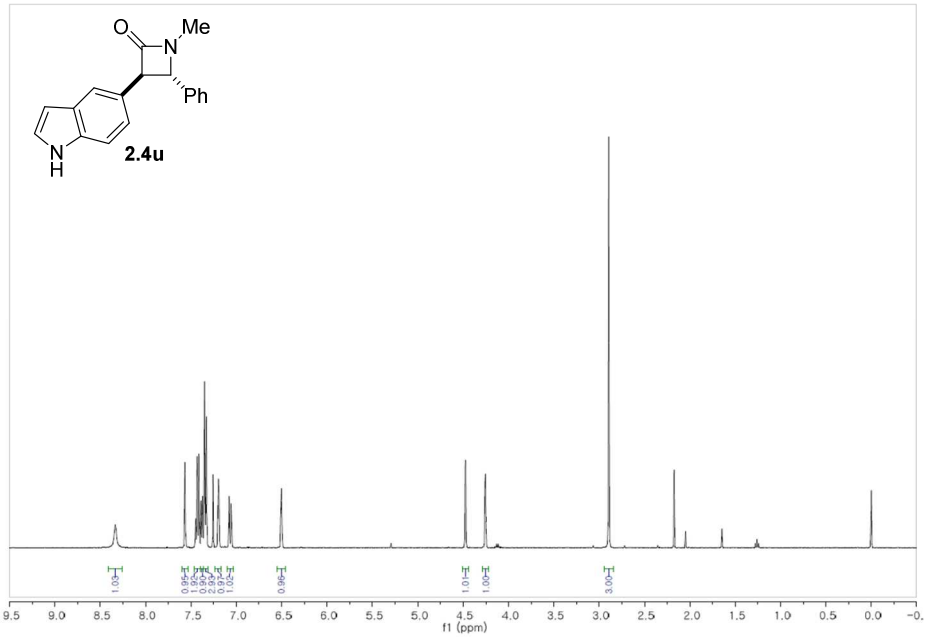
137.6
133.6
132.9
132.7
129.4
128.9
128.5
128.0
126.2
125.3
77.5
77.2
76.9
66.1
65.6
27.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
Me
Ph
N
H
2.4u
1.03
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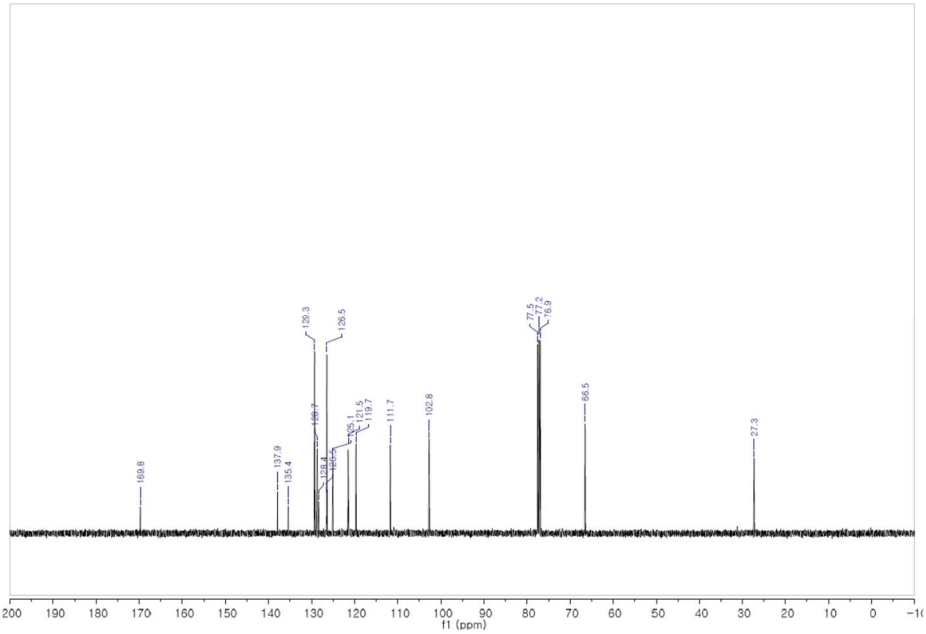
0.96
0.96
2.99
0.96
1.02
0.98
1.01
1.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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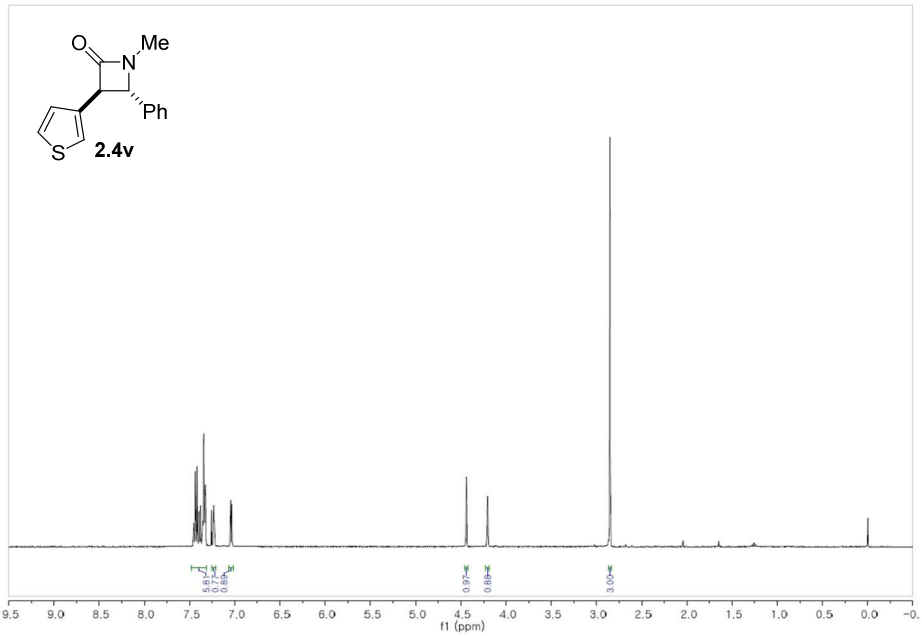
129.3
128.7
126.5
125.1
121.5
119.7
111.7
102.8
77.5
77.2
76.9
66.5
27.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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N
Me
Ph
S
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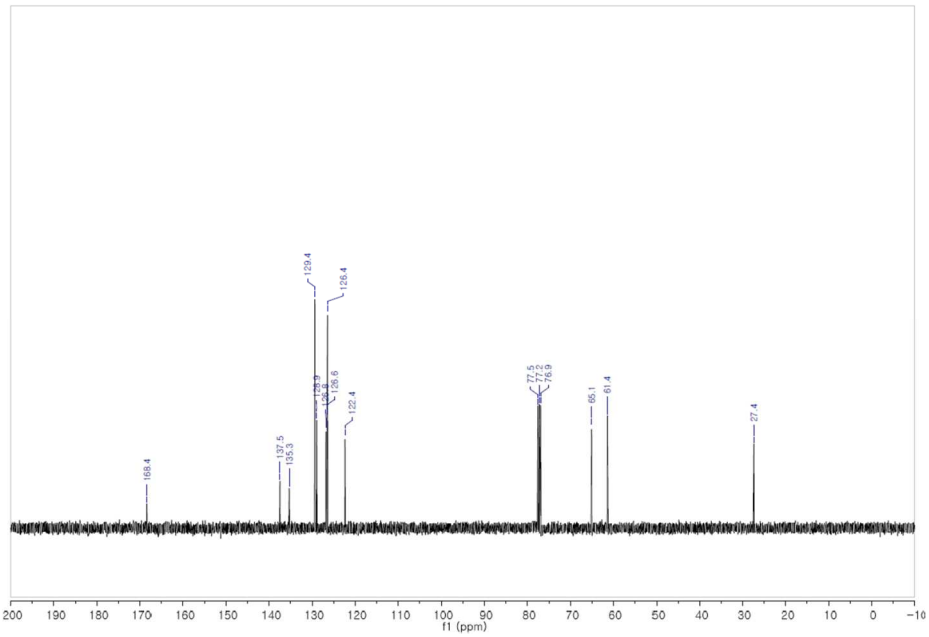
0.71
0.85
0.91
0.88
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)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128.7
126.6
126.4
122.4
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77.2
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65.1
61.4
27.4
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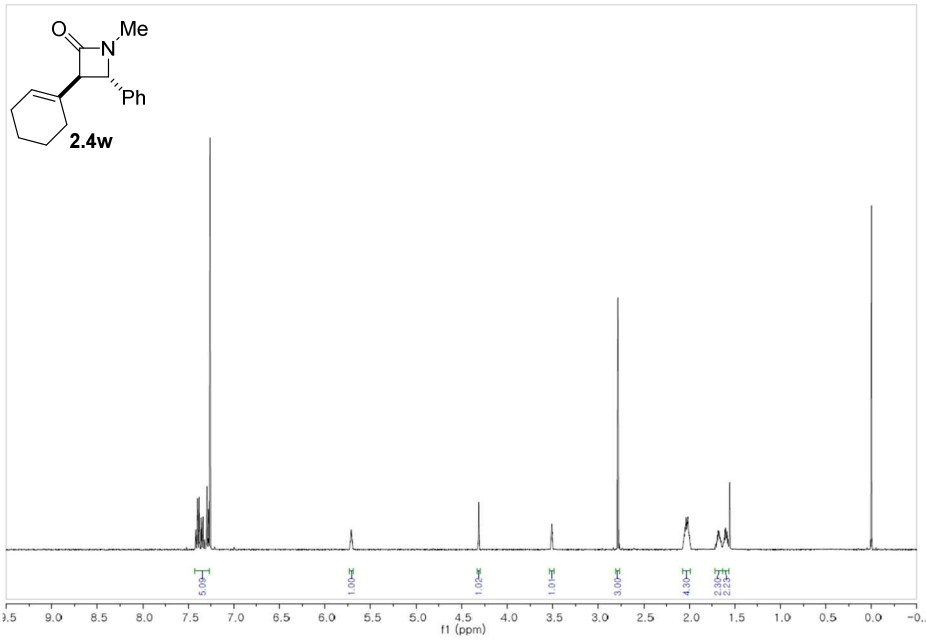
f1 (ppm)


O
N
Me
Ph
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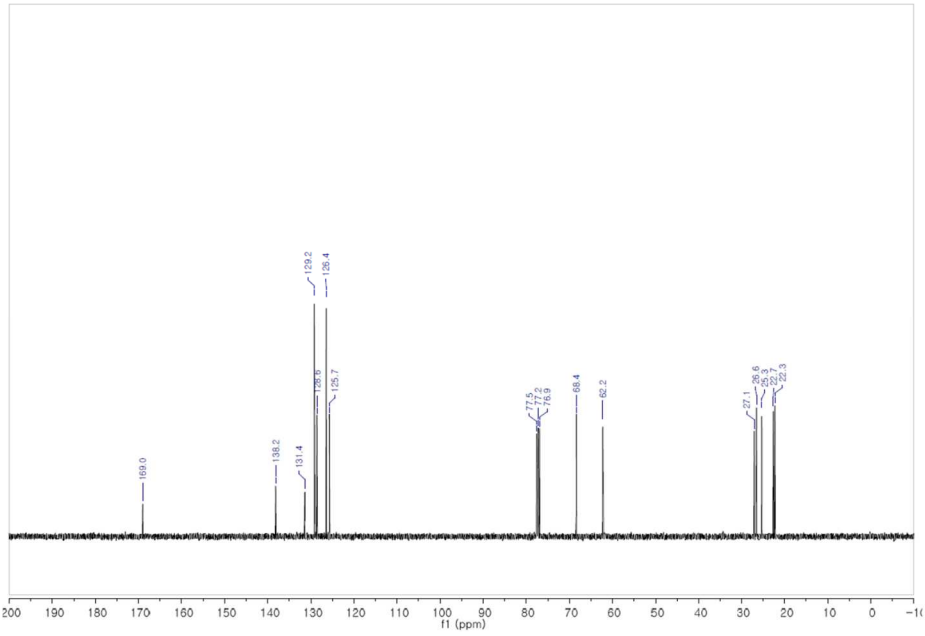
1.01
3.00
4.30
2.30
2.28
f1 (ppm)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138.2
131.4
129.2
128.5
126.4
125.7
77.5
77.2
76.9
68.4
62.2
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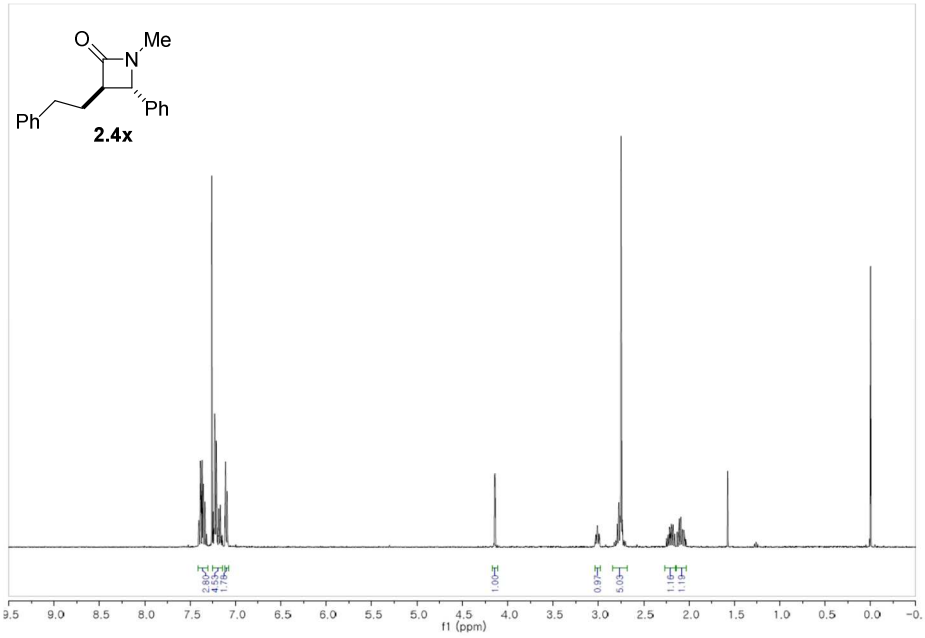
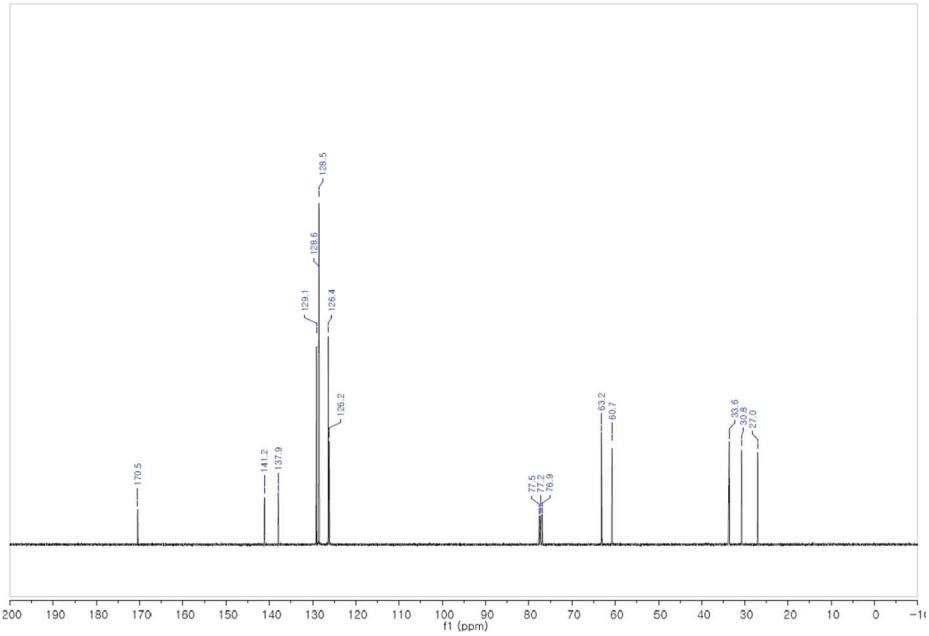
26.6
25.3
22.7
22.3
f1 (ppm)


O
N
Me
Ph
Ph
2.4x
f1 (ppm)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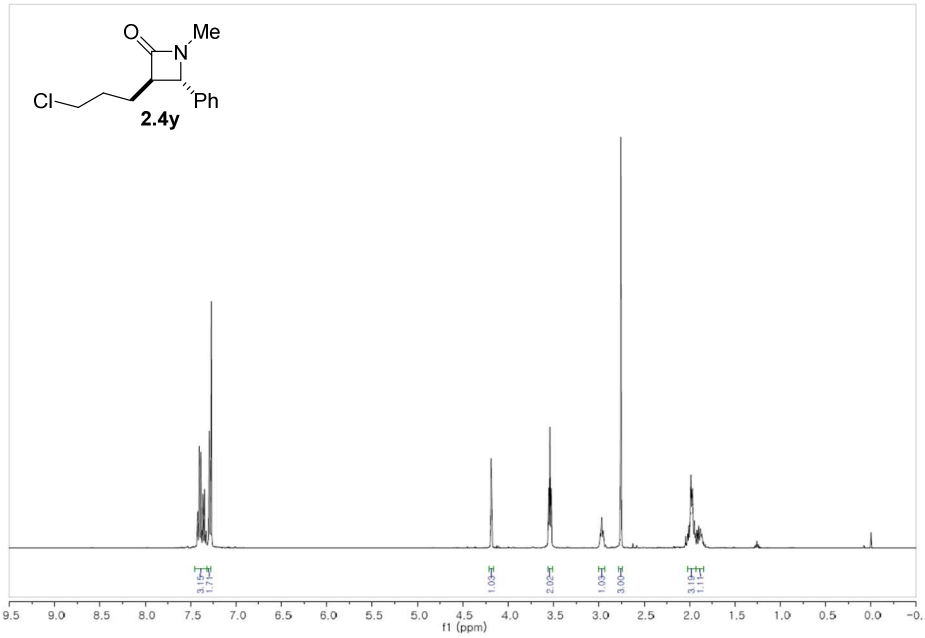
141.2
137.9
129.1
128.6
128.5
126.4
126.2
77.5
77.2
76.9
63.2
60.7
33.6
29.8
27.0
f1 (ppm)


O
N
Me
Cl
Ph
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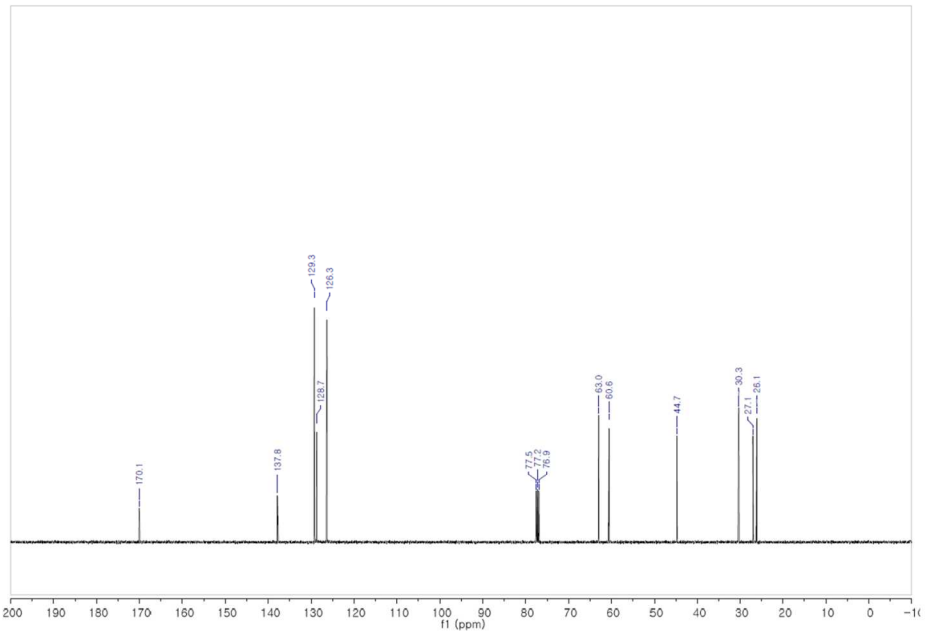
1.03
2.02
1.09
3.00
3.19
1.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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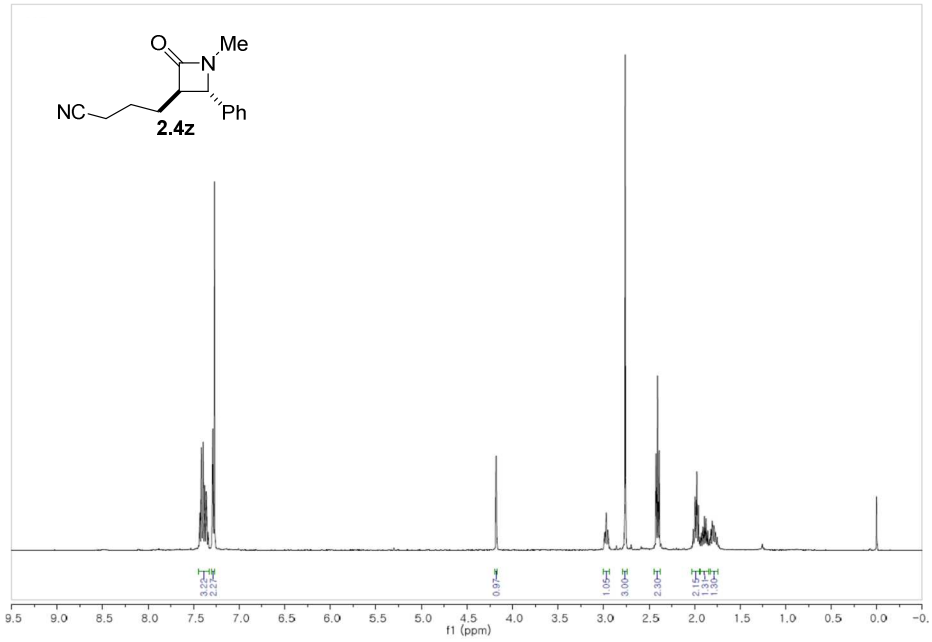
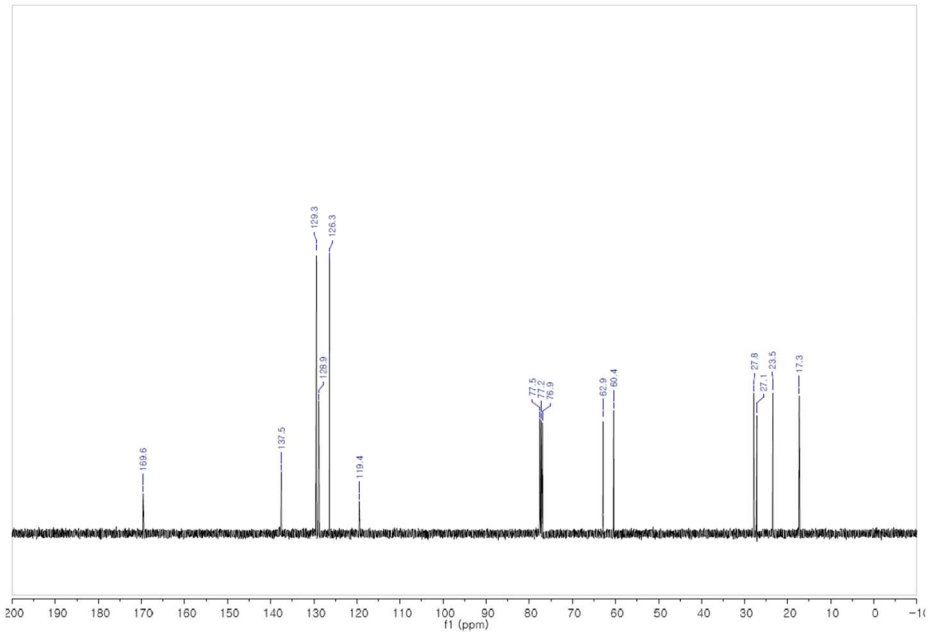
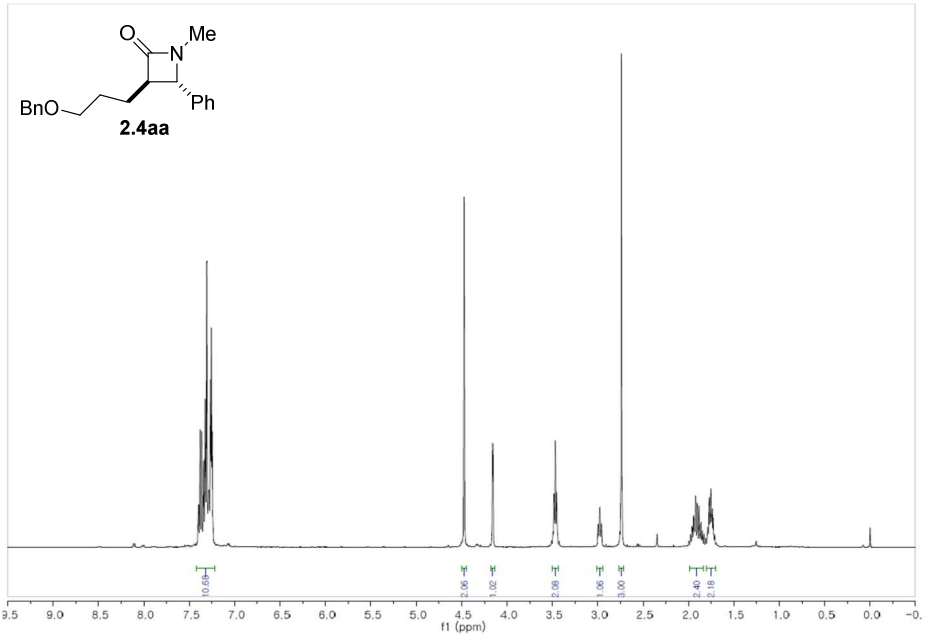
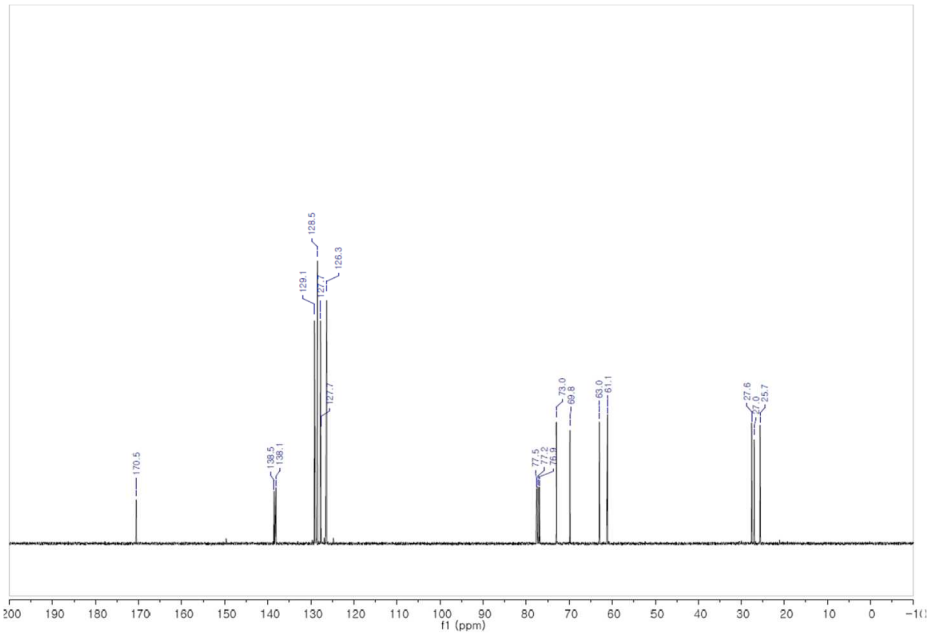
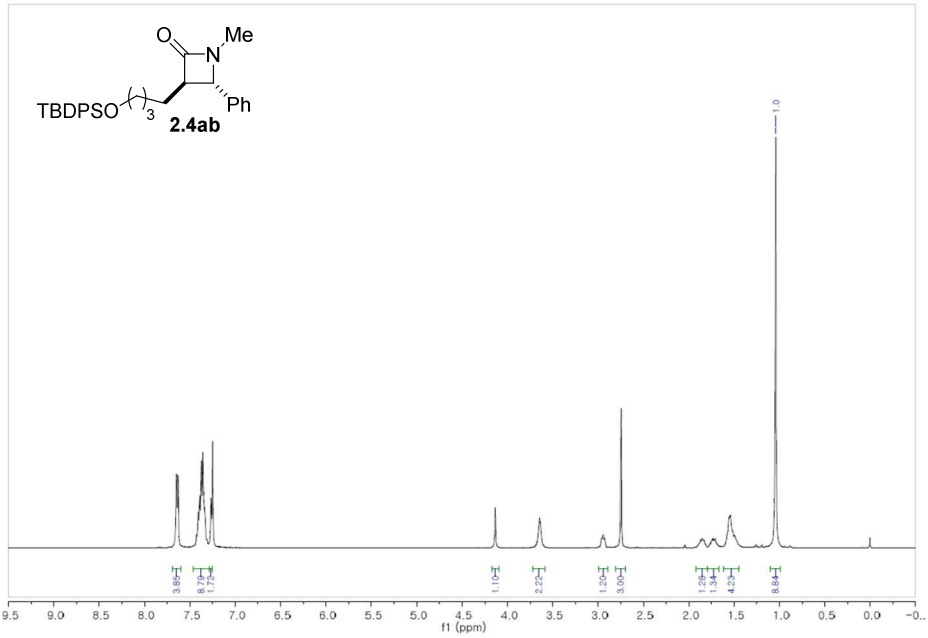
129.3
128.7
126.3
77.5
77.2
76.9
63.0
60.6
44.7
30.3
27.1
26.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

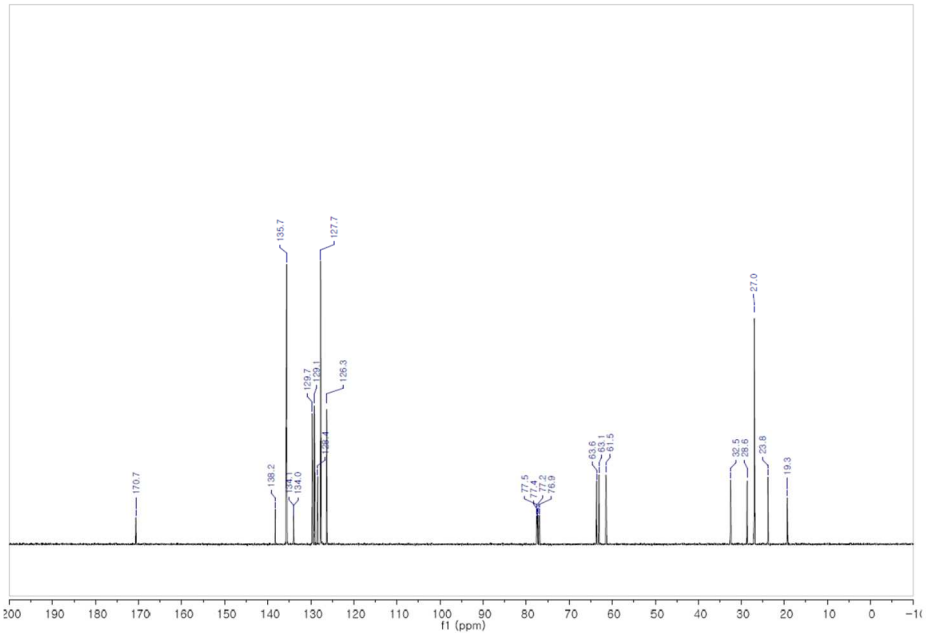

O
N
Me
NC
Ph
2.4z
f1 (ppm)

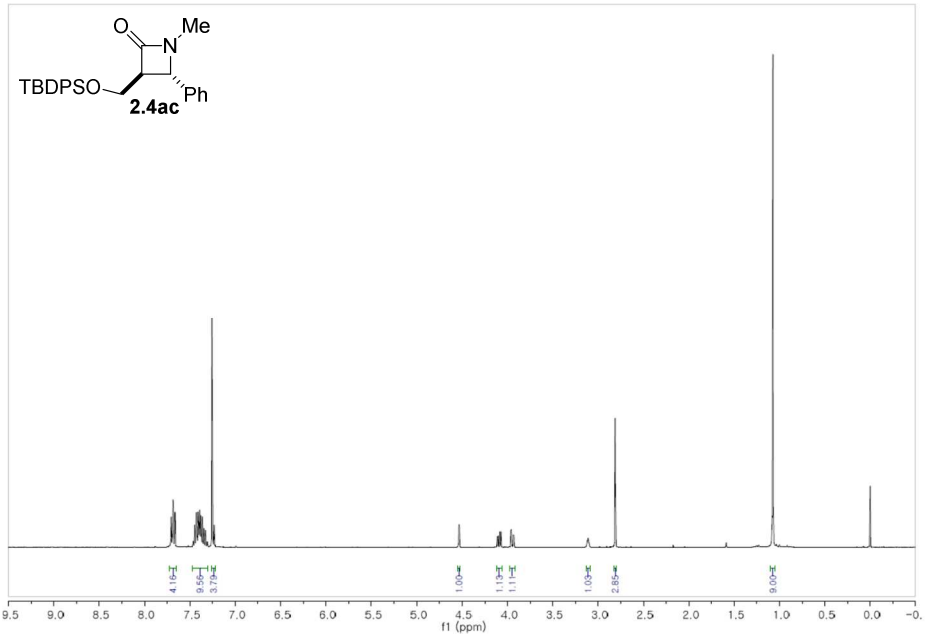

169.6
137.5
129.3
126.3
128.9
119.4
77.5
77.2
76.9
62.9
60.4
27.8
27.1
23.5
17.3
f1 (ppm)

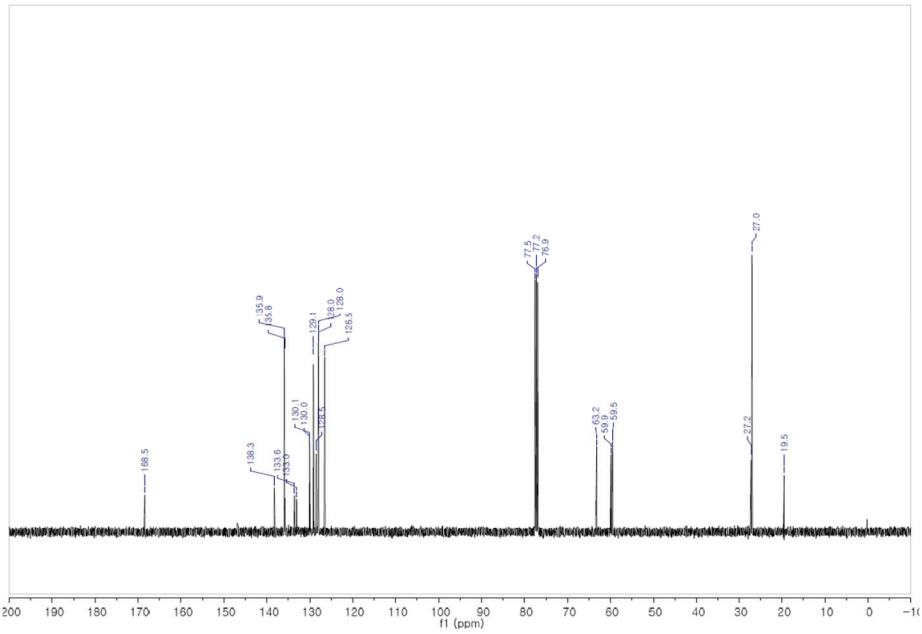

O
N
Me
BnO
Ph
2.4aa
10.68
2.06
1.02
2.08
1.06
3.00
2.40
2.18
f1 (ppm)

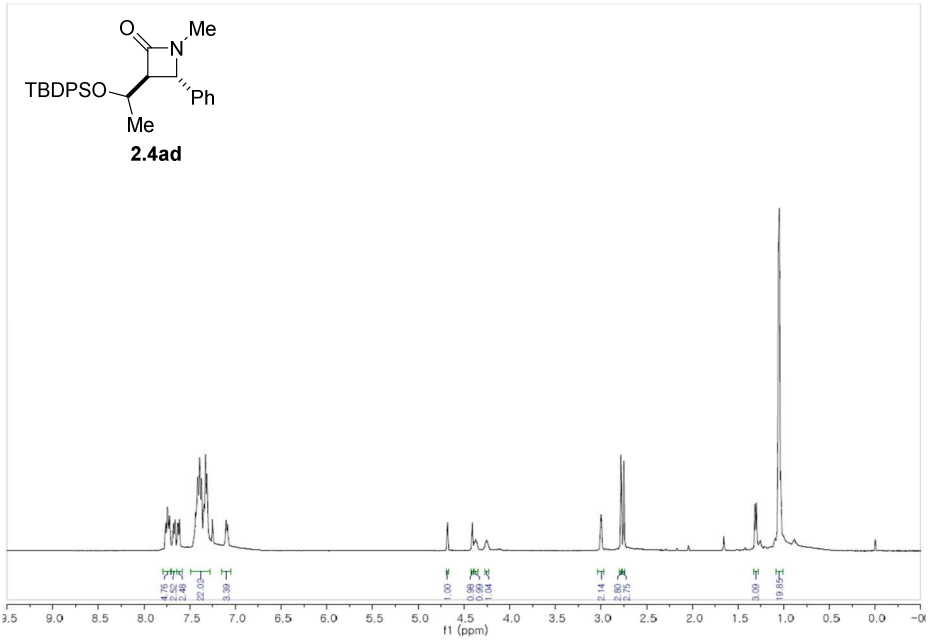

170.5
138.5
138.1
129.1
128.5
127.4
126.3
127.7
77.5
77.2
76.9
73.0
69.8
63.0
61.1
27.6
27.0
25.7
f1 (ppm)

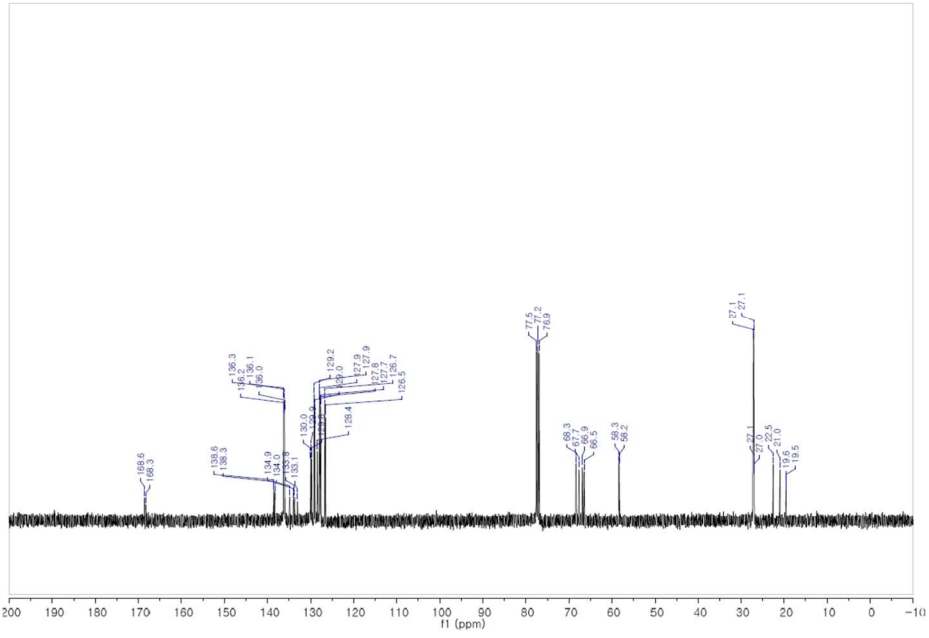

O
N
Me
Ph
TBDPSO
3
2.4ab
1.0
3.86
8.79
1.72
1.10
2.22
1.20
3.00
1.26
1.94
4.25
8.84
f1 (ppm)

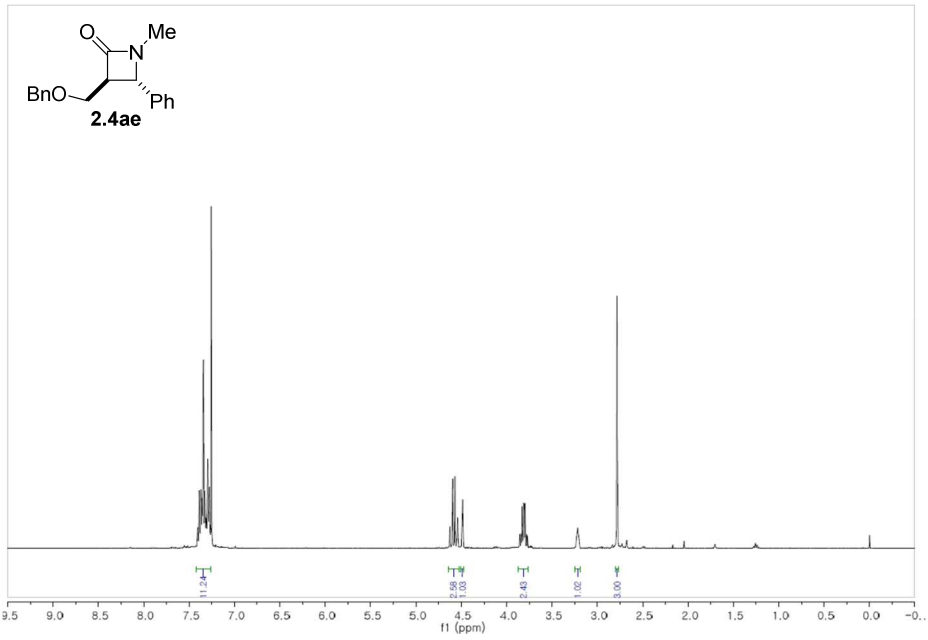

170.7
138.2
135.7
134.1
134.0
129.7
129.1
127.7
126.3
126.4
77.5
77.4
77.2
76.9
63.6
63.1
61.5
32.5
28.6
27.0
23.8
19.3
f1 (ppm)

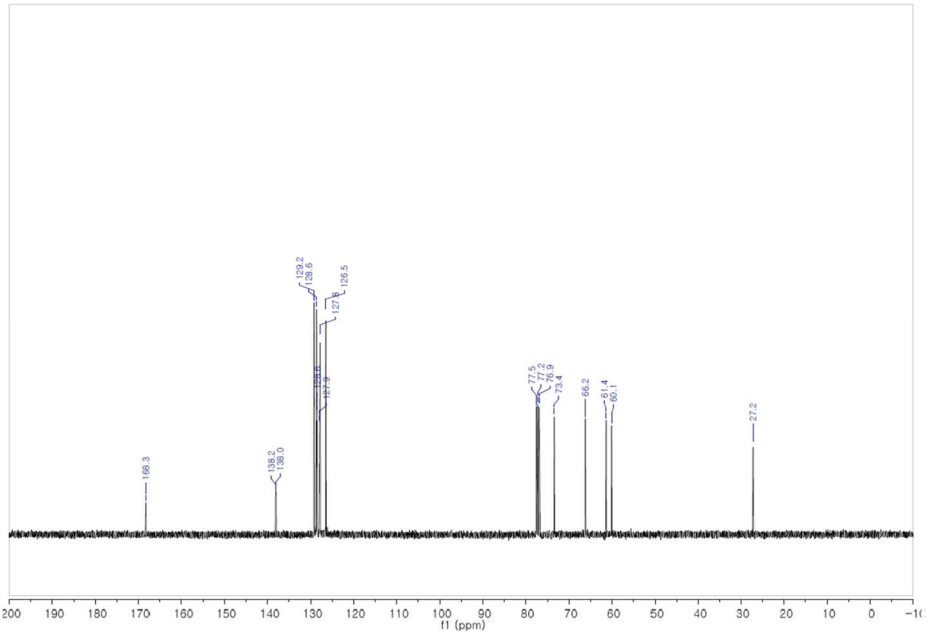

O
N
Me
TBDPSO
Ph
2.4ac
4.16
9.58
3.79
1.00
1.13
1.11
1.03
2.85
9.00
f1 (ppm)

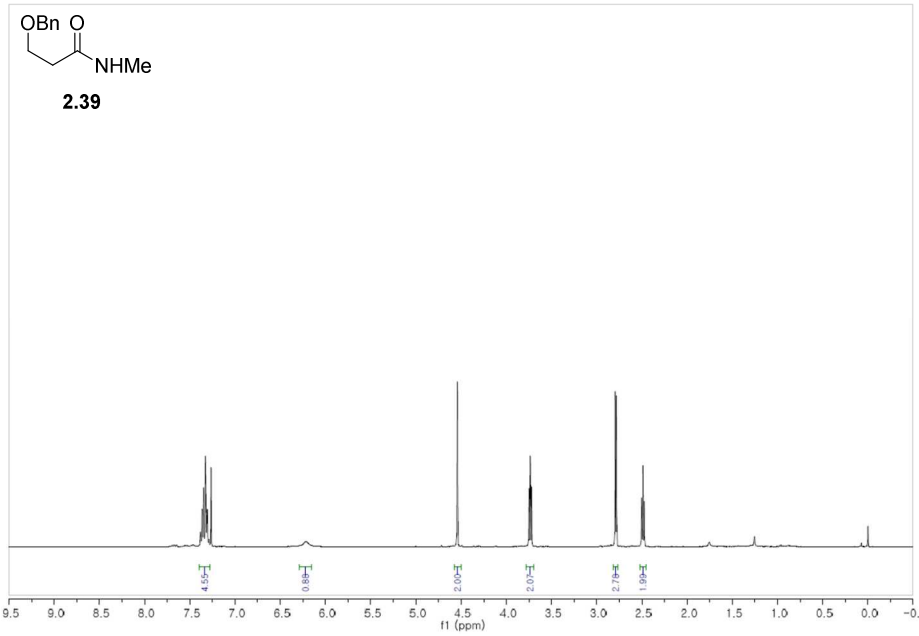

168.5
138.3
135.9
135.8
133.6
133.0
130.1
130.0
129.1
128.5
128.0
128.0
126.5
77.5
77.2
76.9
63.2
59.9
59.5
27.0
27.2
19.5
f1 (ppm)

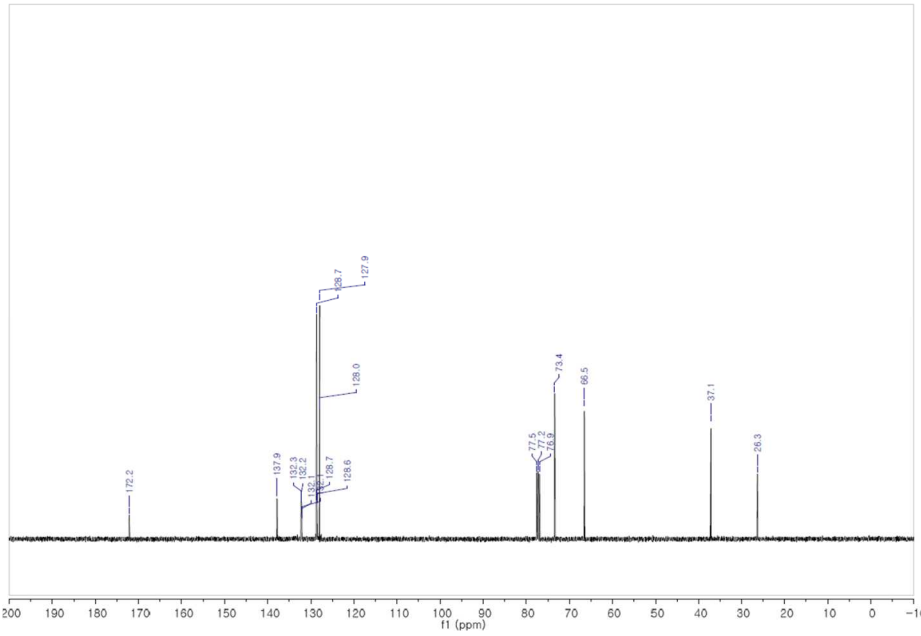

O
N
Me
TBDPSO
Ph
Me
2.4ad
f1 (ppm)

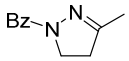

f1 (ppm)


O
N
Me
BnO
Ph
2.4ae
11.24
2.58
1.03
2.43
1.02
3.00
f1 (ppm)

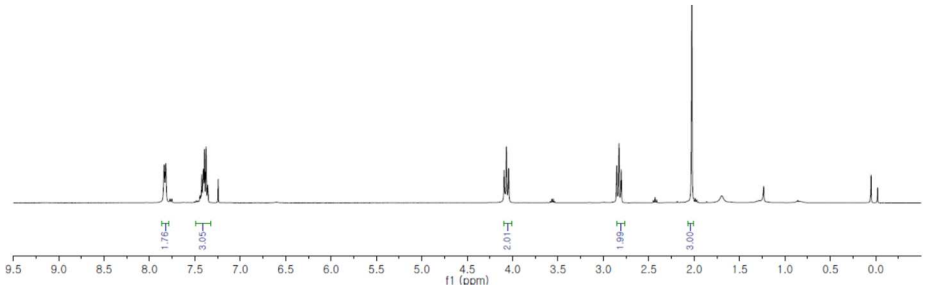

129.2
128.6
126.5
128.3
127.9
77.5
77.2
76.9
73.4
66.2
61.4
60.1
27.2
168.3
138.2
138.0
f1 (ppm)

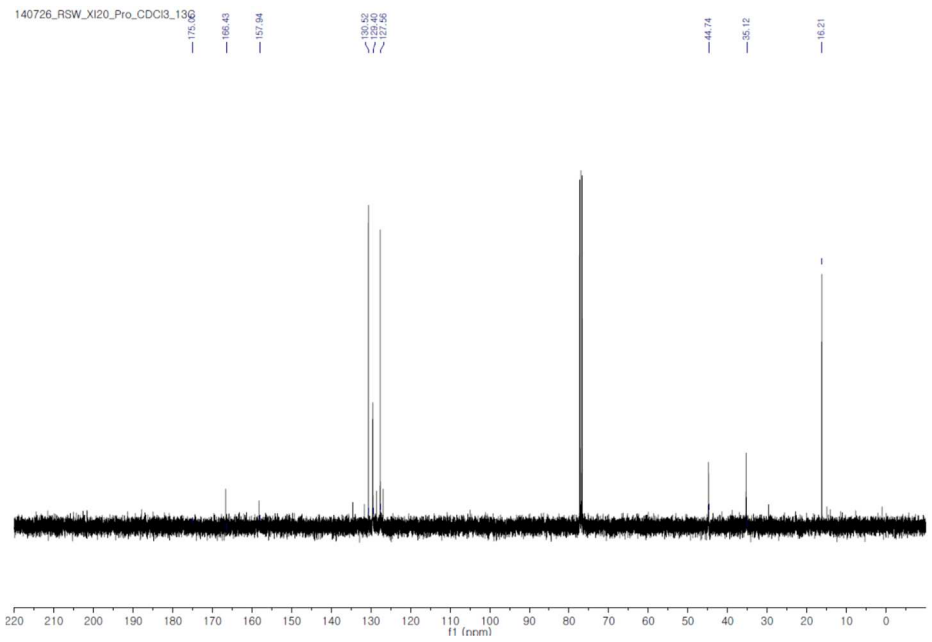

OBn O
NHMe
2.39
4.55
0.89
2.00
2.01
2.79
1.99
f1 (ppm)

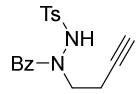

172.2
137.9
132.3
132.2
128.7
128.6
128.0
127.9
77.5
77.2
76.8
73.4
66.5
37.1
26.3
f1 (ppm)


Bz
N
N

2.63a

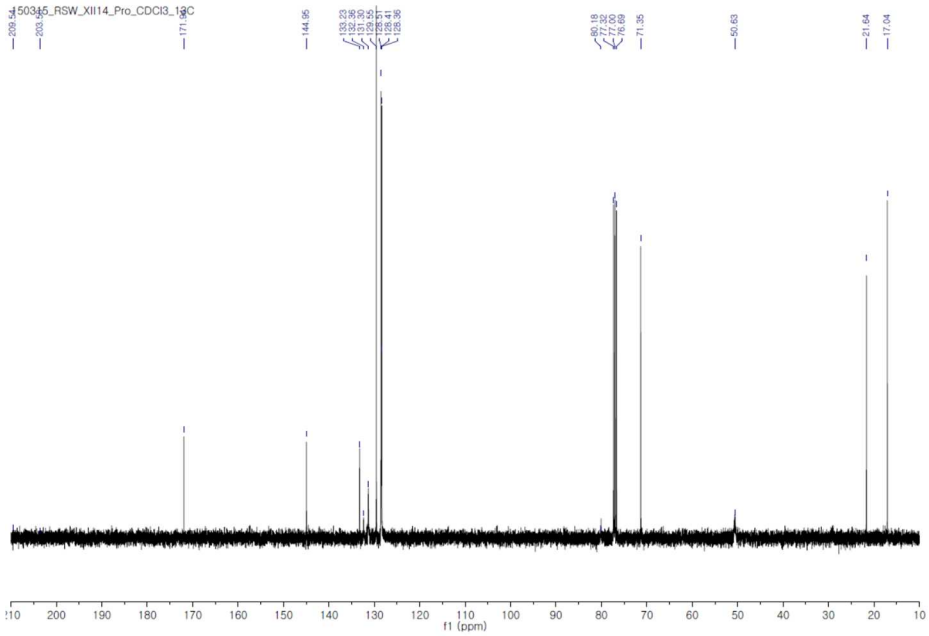

1.76
3.05
2.01
1.99
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

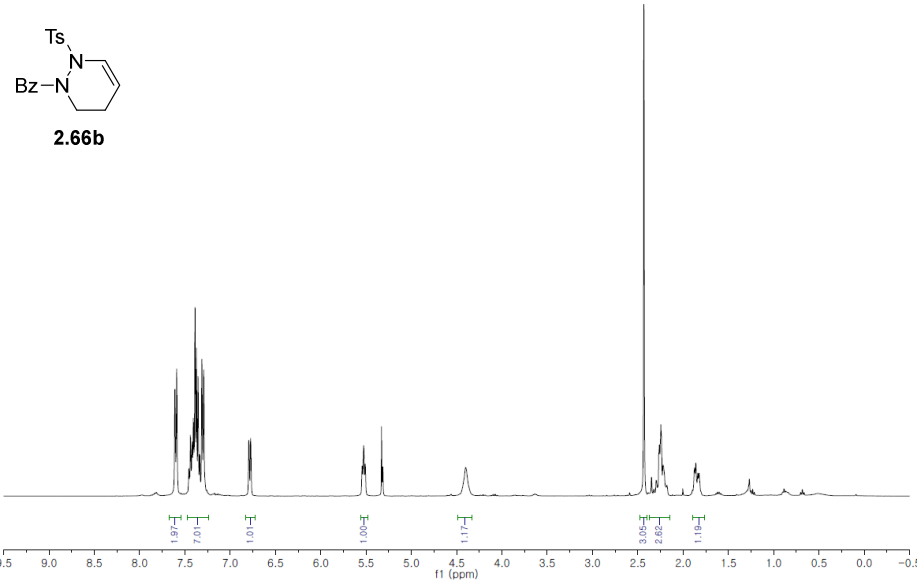

140726_RSW_XI20_Pro_CDCl3_13C
175.00
166.43
157.94
130.52
129.40
127.56
44.74
35.12
16.21
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

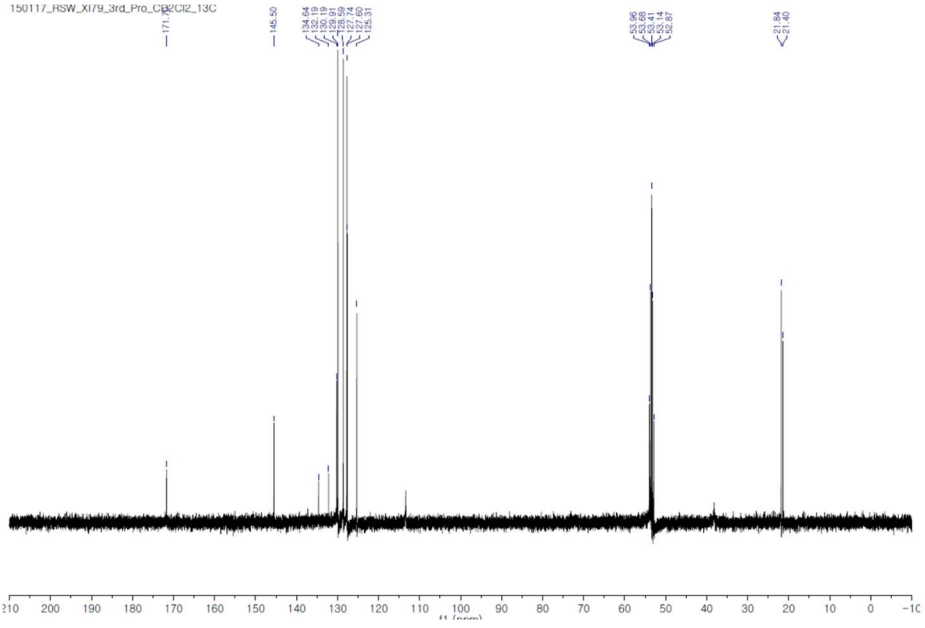

Ts
NH
Bz—N

2.60b

0.97
1.88
1.04
1.77
1.99
2.17
2.07
1.88
3.00
0.73
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


150315_RSW_XII14_Pro_CDCl3_13C
209.54
203.57
171.46
144.95
133.23
132.96
131.30
129.55
128.51
128.41
126.36
80.18
77.32
77.00
76.69
71.35
50.63
21.64
17.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

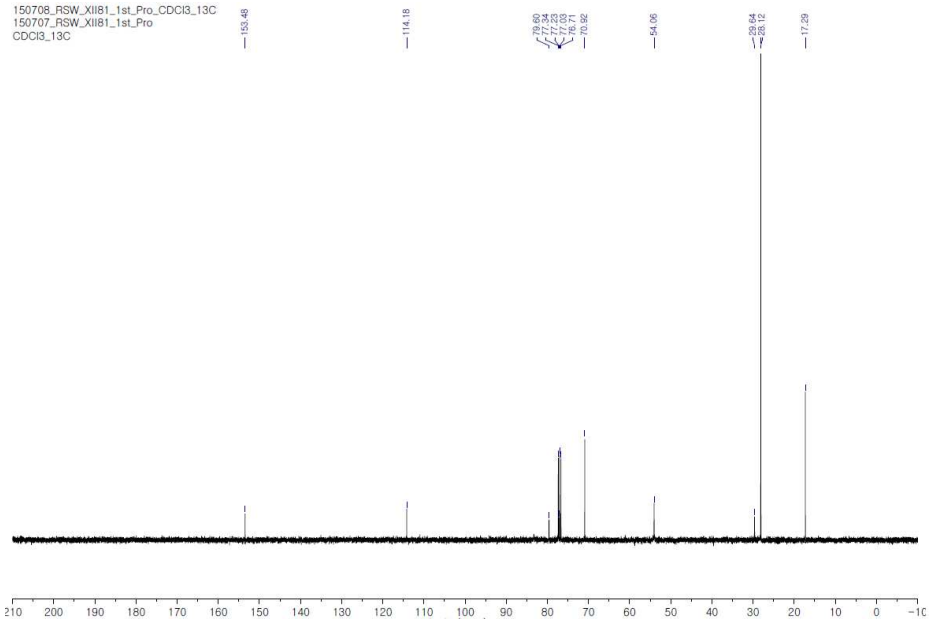

Ts
N
Bz–N
2.66b
1.97
7.01
1.01
1.00
1.17
3.05
2.62
1.19
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

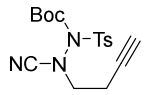

150117_RSW_XI79_3rd_Pro_CD2Cl2_13C
171.13
145.50
134.64
132.19
130.91
130.07
128.59
127.74
127.60
125.31
53.86
53.68
53.41
53.14
52.87
21.84
21.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


Boc
NH
NC–N

S2.3

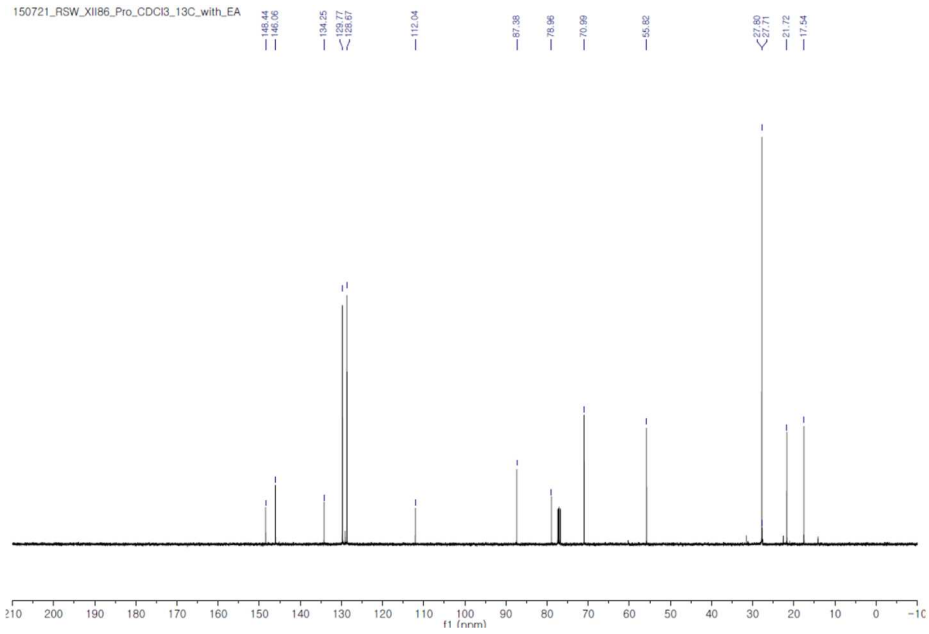
1.00
1.87
1.96
0.92
8.90
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

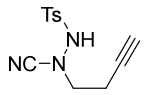

150708_RSW_XII81_1st_Pro_CDCl3_13C
150707_RSW_XII81_1st_Pro
CDCl3_13C
153.48
114.18
77.34
77.23
77.03
76.71
70.92
54.06
29.64
28.12
17.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10


Boc
N–Ts
NC–N

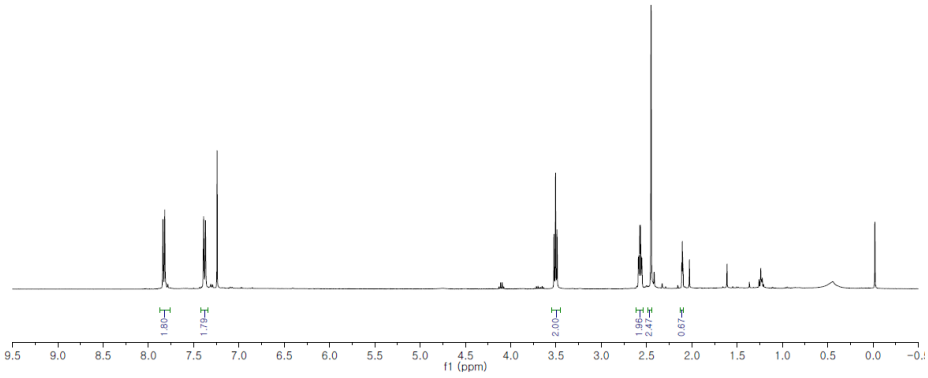
S2.4

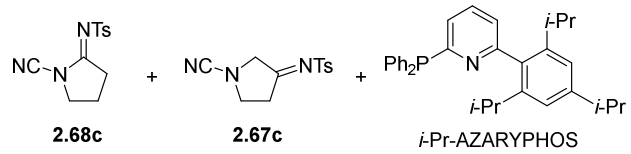
1.77
1.91
2.00
2.04
3.18
0.84
9.04
f1 (ppm)


150721_RSW_XII86_Pro_CDCl3_13C_with_EA
146.44
146.06
134.25
129.77
128.67
112.04
87.38
78.96
70.99
55.82
27.80
27.71
21.72
17.54
f1 (ppm)

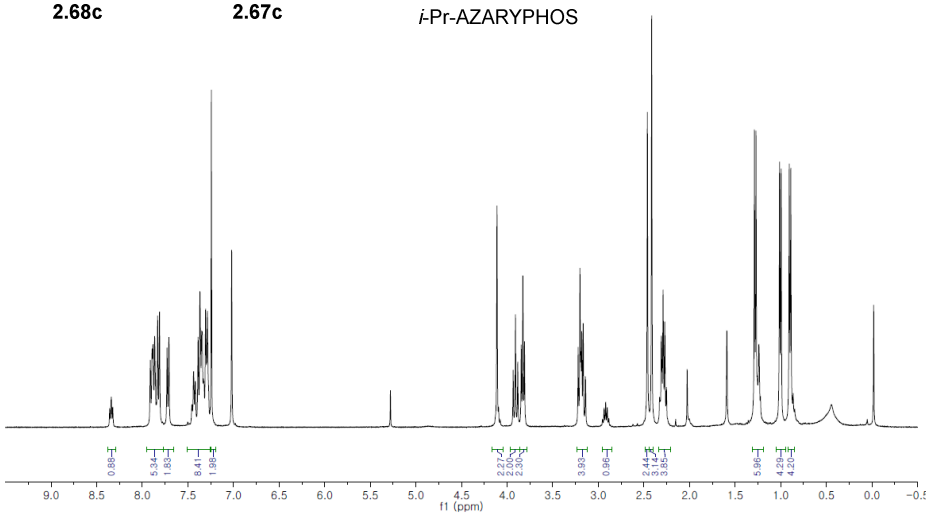

Ts
NH
NC–N

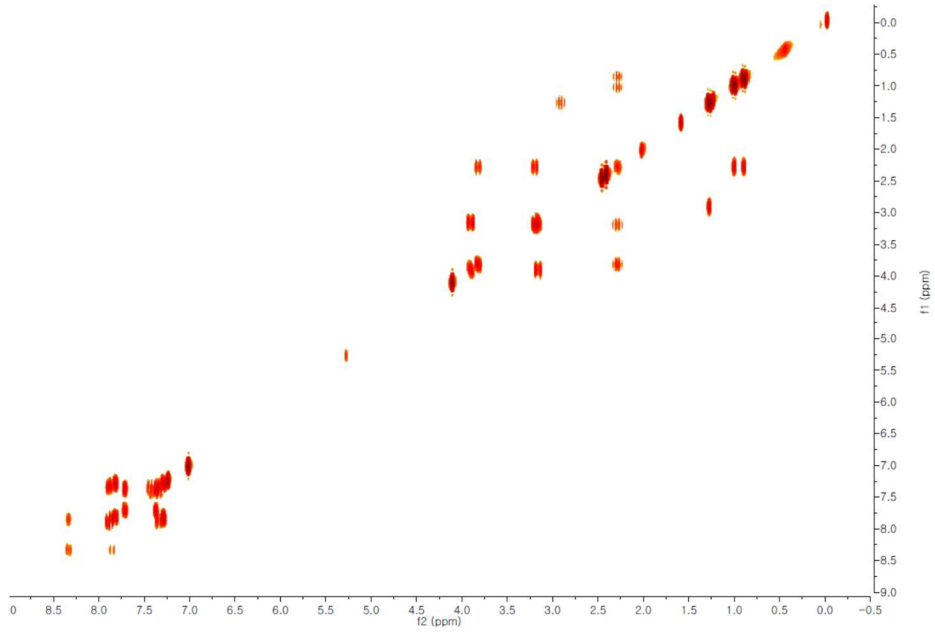
2.60c

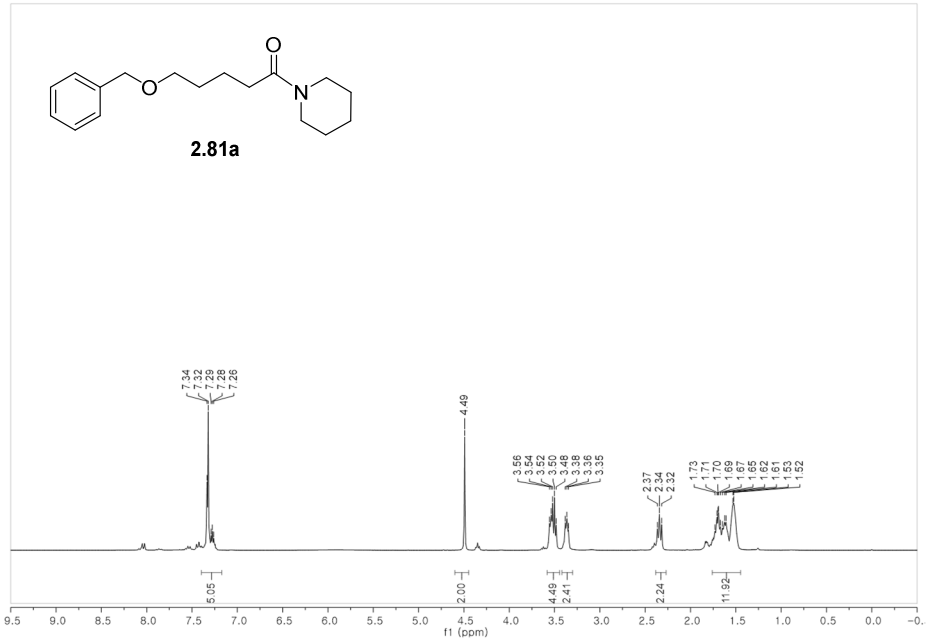

1.80
1.79
2.00
1.96
2.47
0.67
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

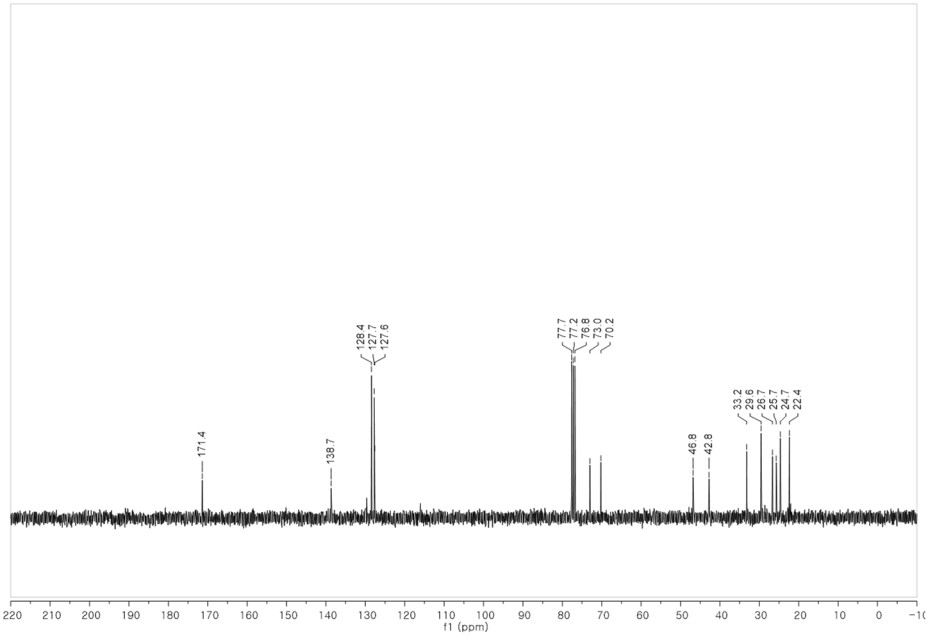


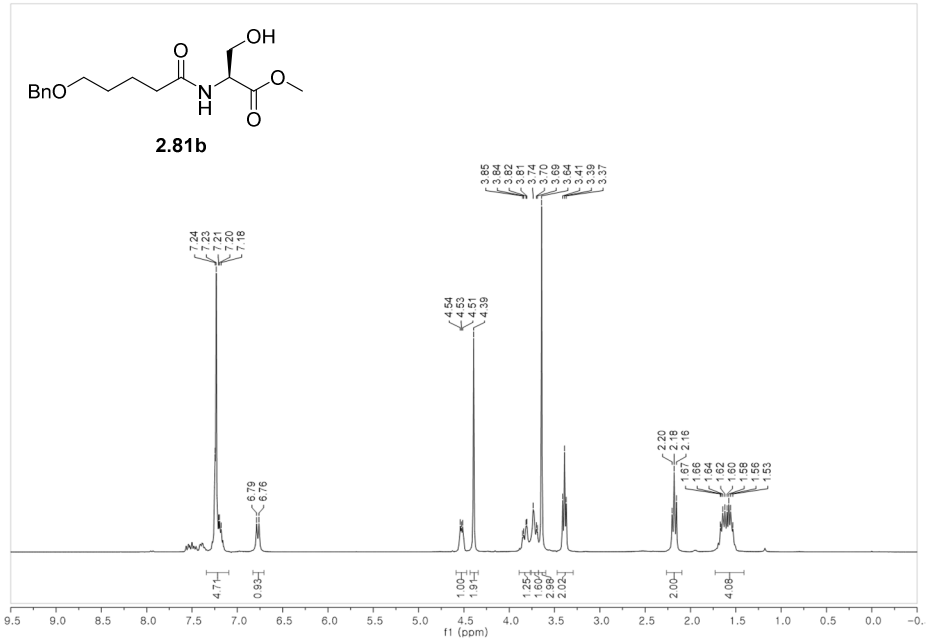
2.68c **2.67c** *i*-Pr-AZARYPHOS

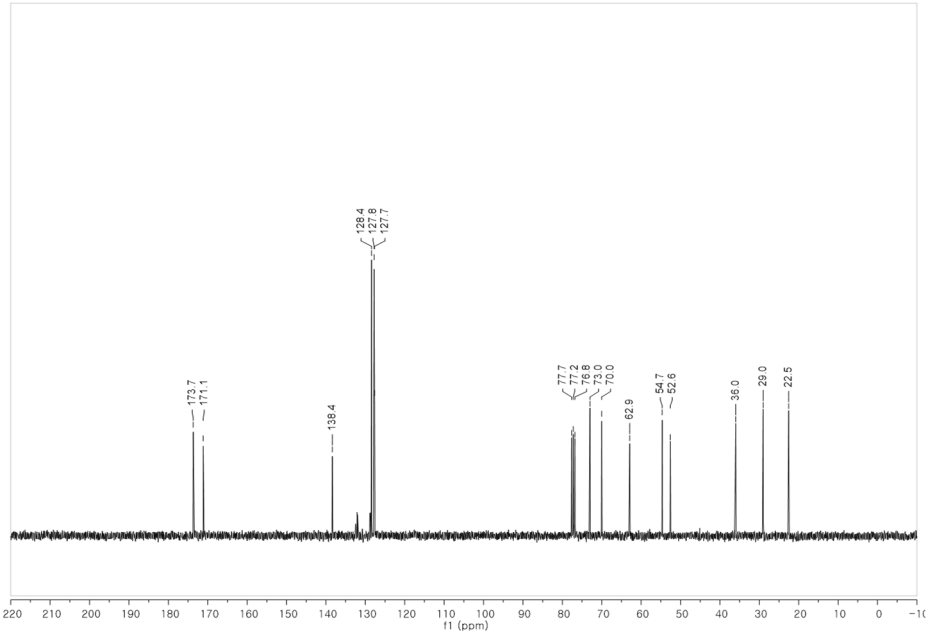


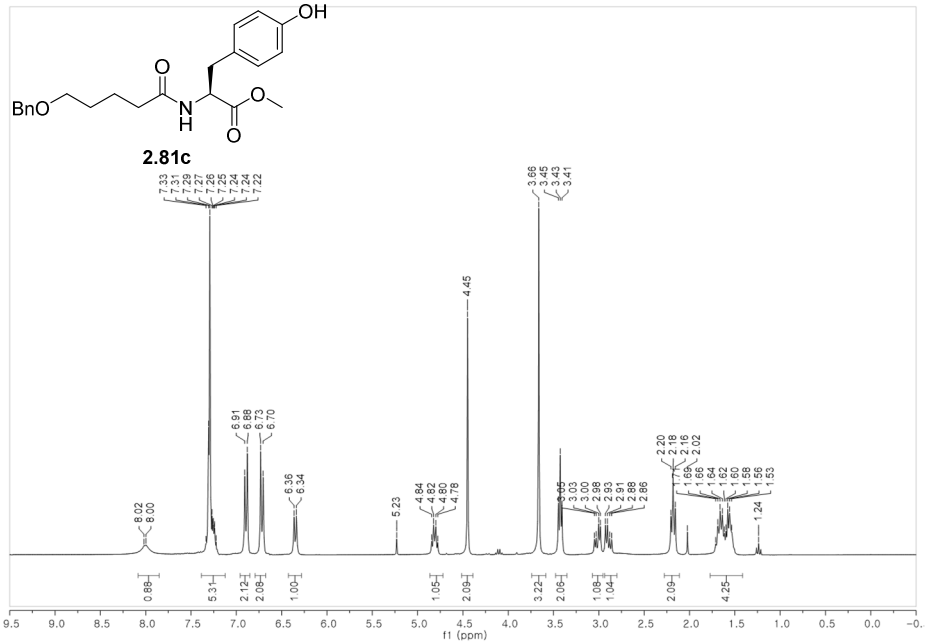



O
O
N
2.81a
7.34
7.32
7.30
7.28
7.26
4.49
3.56
3.54
3.52
3.50
3.48
3.38
3.36
3.35
2.37
2.34
2.32
1.73
1.71
1.70
1.69
1.67
1.65
1.62
1.61
1.53
1.52
5.05
2.00
4.46
2.41
2.24
11.92
f1 (ppm)


171.4
138.7
128.4
127.7
127.6
77.7
77.2
76.8
73.0
70.2
46.8
42.8
33.2
29.6
26.7
25.7
24.7
22.4
f1 (ppm)


BnO
O
N
H
OH
O
O
2.81b
3.85
3.84
3.82
3.81
3.74
3.70
3.69
3.64
3.41
3.39
3.37
7.24
7.23
7.21
7.20
7.18
4.54
4.53
4.51
4.39
2.20
2.18
2.16
1.67
1.66
1.64
1.62
1.60
1.58
1.55
1.53
6.79
6.76
4.71
0.93
1.00
1.91
1.25
1.60
2.89
2.02
2.00
4.08
f1 (ppm)


128.4
127.8
127.7
173.7
171.1
138.4
77.7
77.2
76.8
73.0
70.0
62.9
54.7
52.6
36.0
29.0
22.5
f1 (ppm)


OH
O
BnO
N
H
O
O
2.81c
7.33
7.31
7.29
7.27
7.26
7.25
7.24
7.24
7.22
8.02
8.00
6.91
6.88
6.73
6.70
6.36
6.34
5.23
4.84
4.82
4.80
4.78
4.45
3.66
3.45
3.43
3.41
3.05
3.03
3.00
2.98
2.93
2.91
2.88
2.86
2.20
2.18
2.16
2.02
1.66
1.64
1.62
1.60
1.58
1.56
1.53
1.24
0.88
5.31
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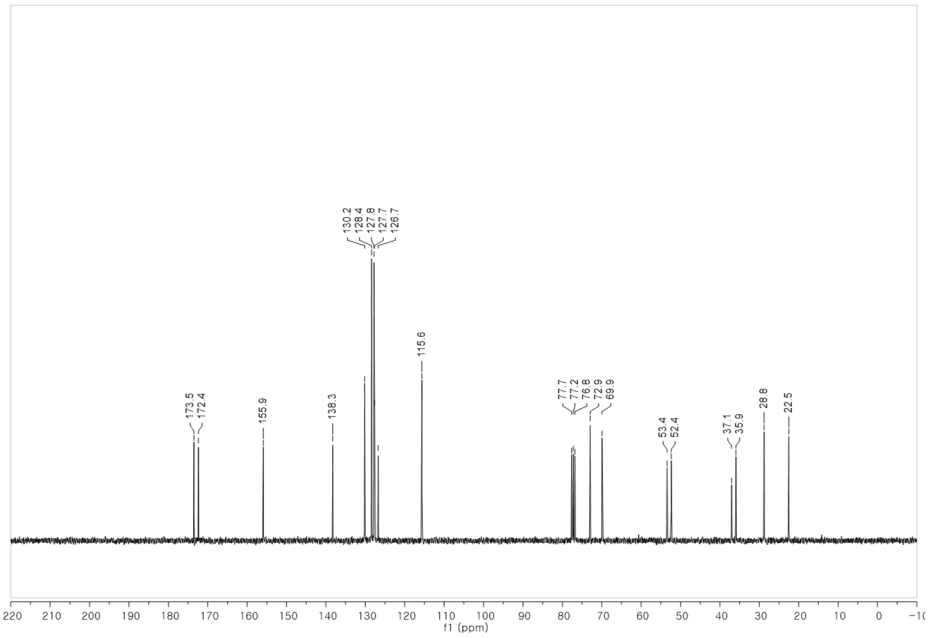
1.05
2.09
3.22
2.06
1.08
1.04
2.09
4.25
f1 (ppm)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127.7
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172.4
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138.3
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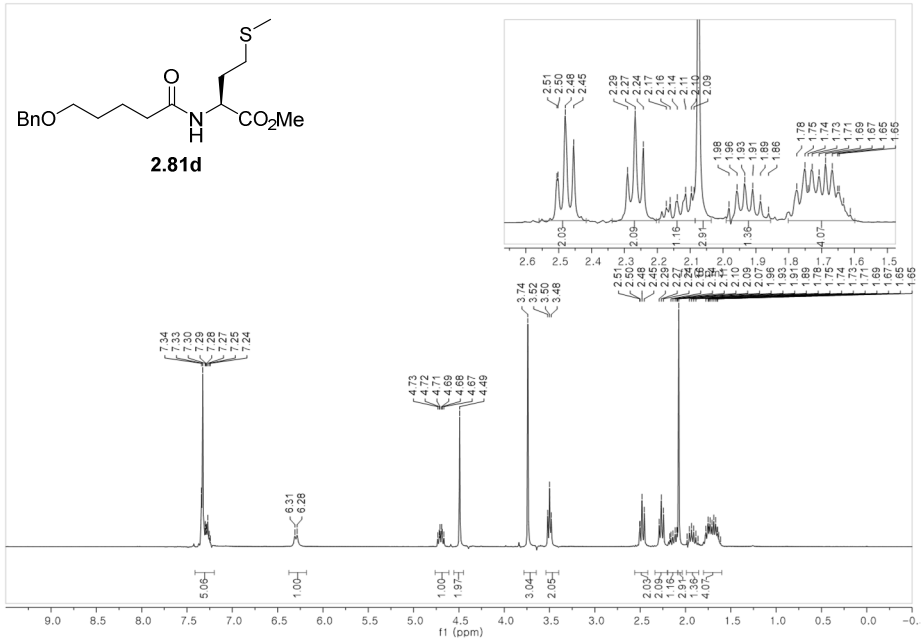
53.4
52.4
37.1
35.9
28.8
22.5
f1 (ppm)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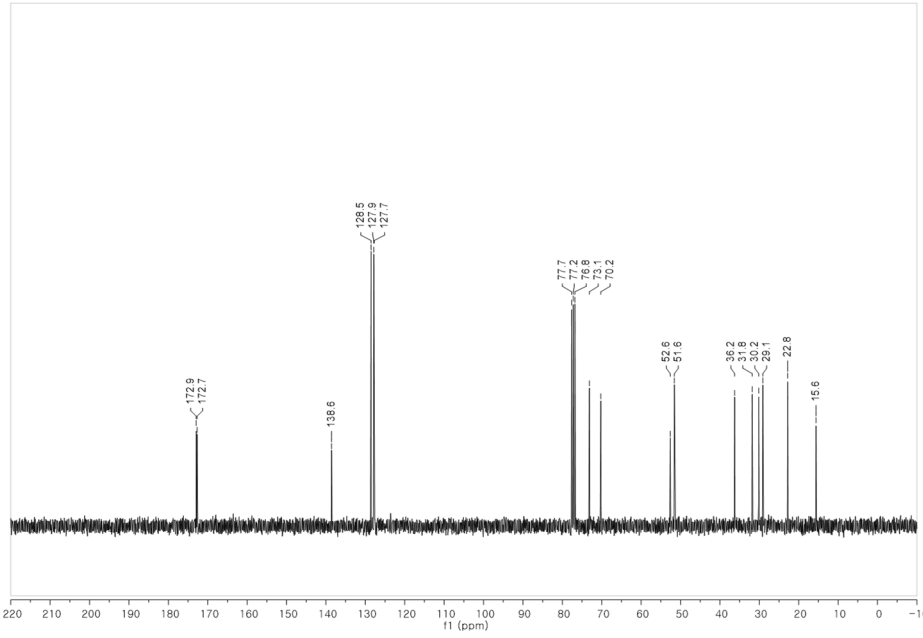
N
H
S
CO2Me
2.81d
f1 (ppm)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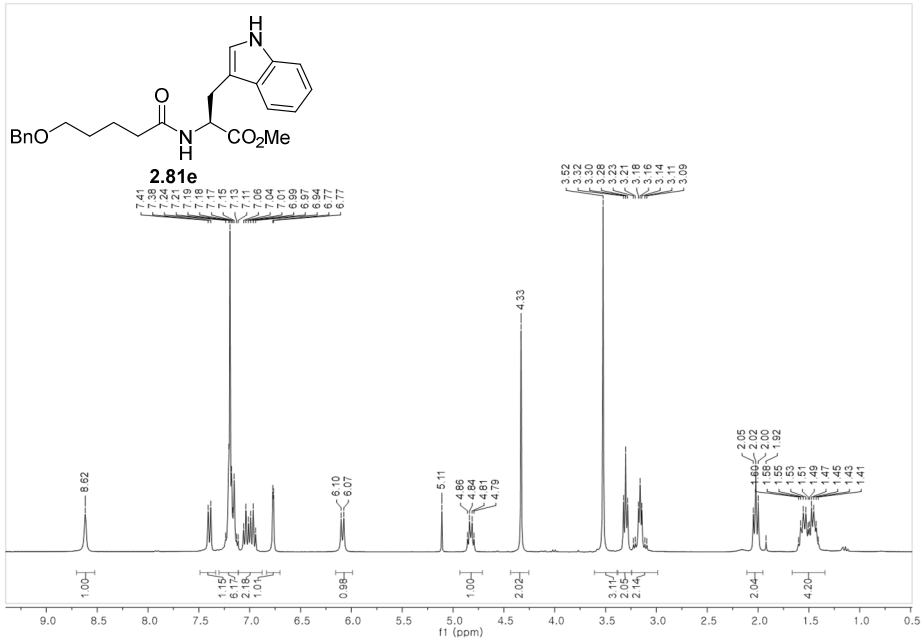
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H
CO2Me
2.81e
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7.41
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7.21
7.19
7.18
7.17
7.15
7.13
7.11
7.06
7.04
7.01
6.99
6.97
6.94
6.77
6.77
6.10
6.07
5.11
4.86
4.84
4.81
4.79
4.33
3.52
3.32
3.30
3.28
3.23
3.21
3.18
3.16
3.14
3.11
3.09
2.05
2.02
2.00
1.92
1.63
1.58
1.55
1.53
1.51
1.49
1.47
1.45
1.43
1.41
1.00
1.15
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2.02
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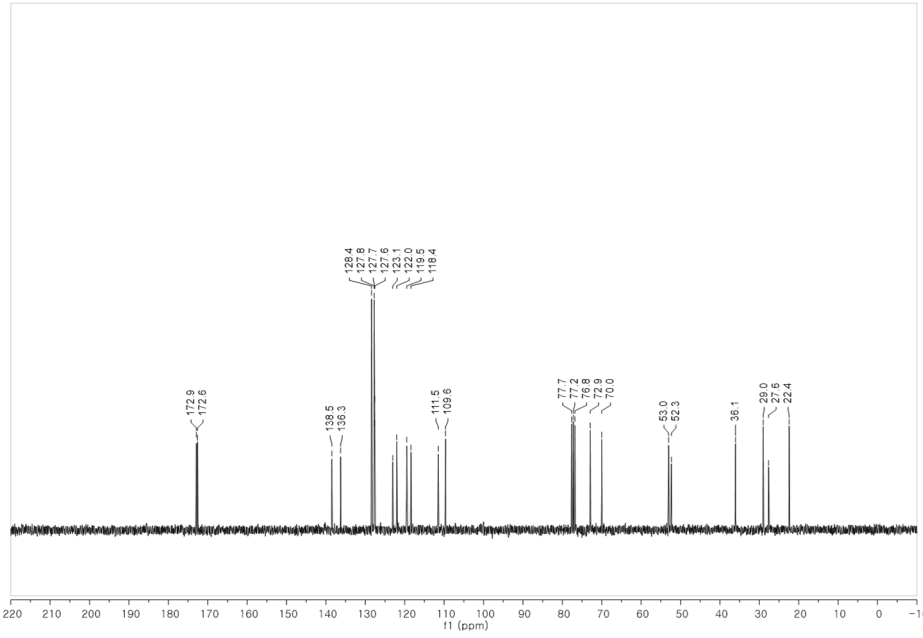
3.05
2.14
2.04
4.20
f1 (ppm)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127.6
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122.0
119.5
118.4
111.5
109.6
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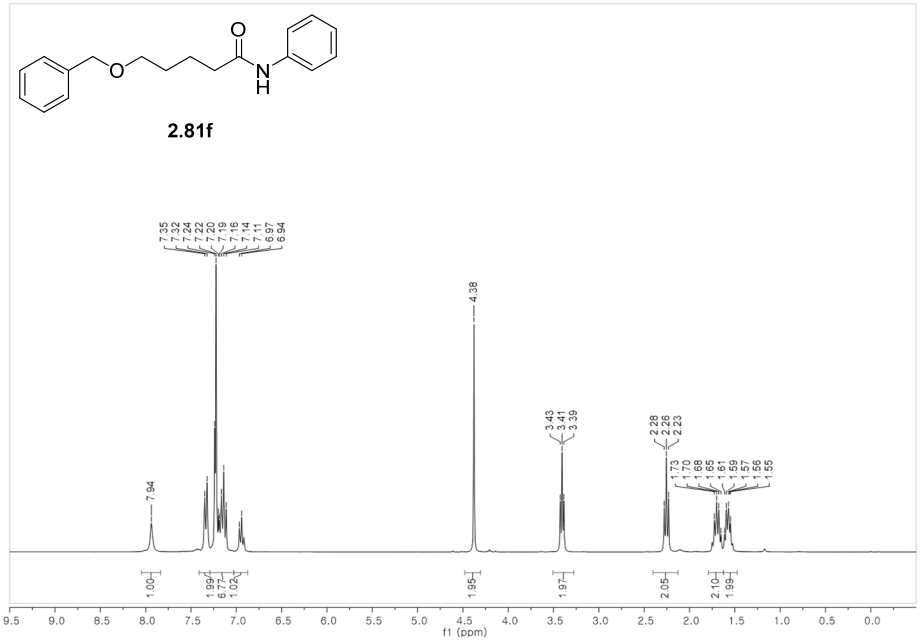
76.8
72.9
70.0
53.0
52.3
36.1
29.0
27.6
22.4
f1 (ppm)


O
O
N
H
2.81f
7.35
7.32
7.24
7.22
7.20
7.19
7.16
7.14
7.11
6.97
6.94
7.94
4.38
3.43
3.41
3.39
2.28
2.26
2.23
1.73
1.70
1.68
1.65
1.61
1.59
1.57
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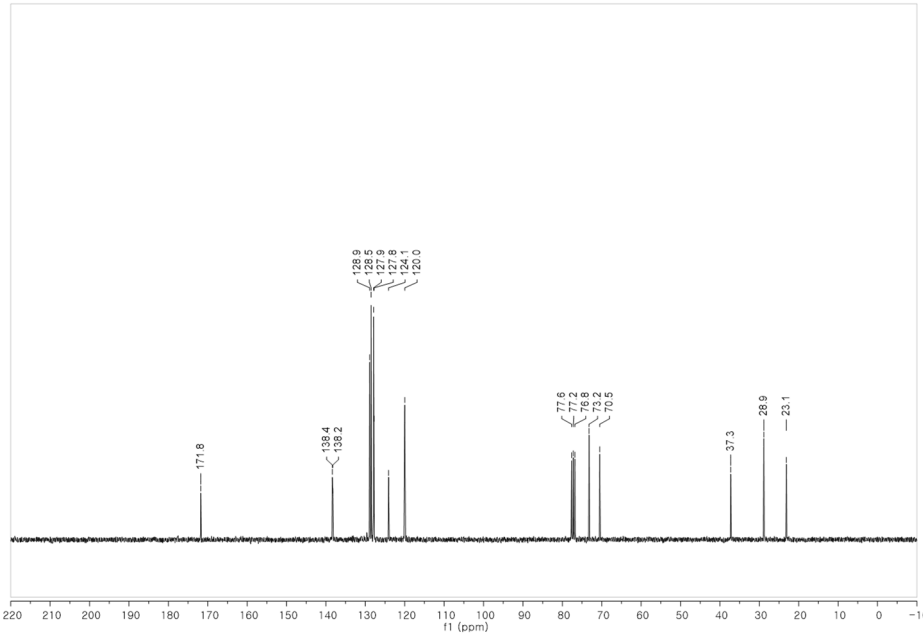
1.95
1.97
2.05
2.10
1.99
f1 (ppm)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127.9
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124.1
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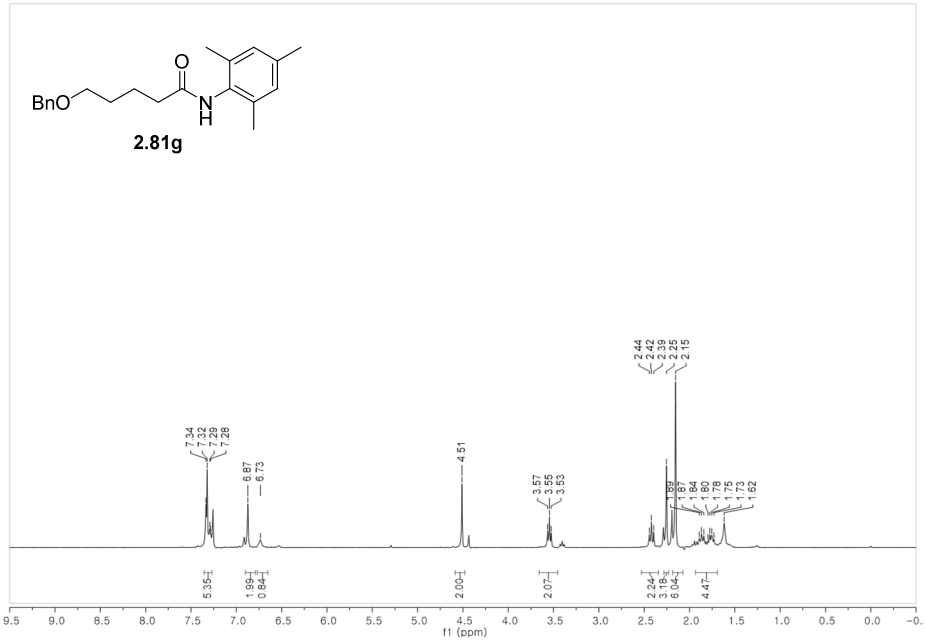
77.6
77.2
76.8
73.2
70.5
37.3
28.9
23.1
f1 (ppm)


BnO
O
N
H
2.81g
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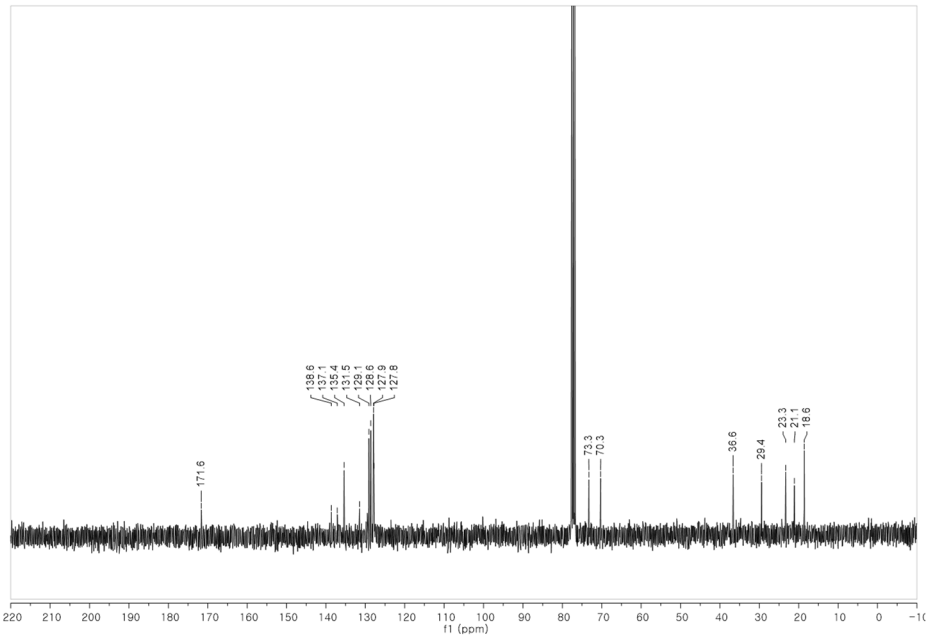
7.28
6.87
6.73
4.51
3.57
3.55
3.53
2.44
2.42
2.39
2.25
2.15
1.89
1.87
1.84
1.80
1.78
1.75
1.73
1.62
5.35
1.99
0.84
2.00
2.07
2.24
3.16
6.04
4.47
f1 (ppm)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135.4
131.5
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127.8
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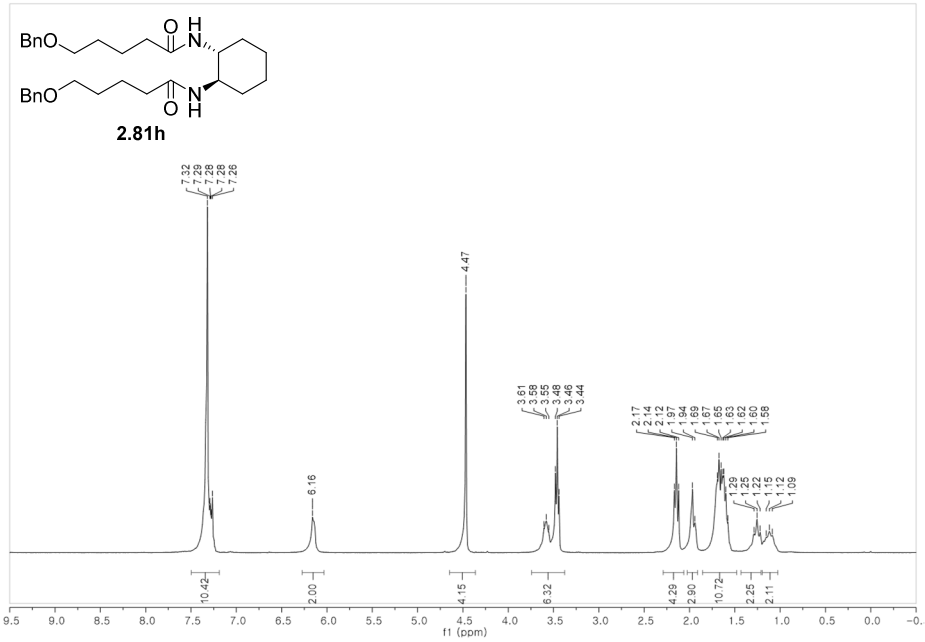
70.3
36.6
29.4
23.3
21.1
18.6
f1 (ppm)


BnO
O
H
N
BnO
N
H
O
2.81h
7.32
7.29
7.28
7.28
7.26
6.16
4.47
3.61
3.58
3.55
3.48
3.46
3.44
2.17
2.14
2.12
1.97
1.94
1.69
1.67
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1.63
1.62
1.60
1.58
1.29
1.25
1.22
1.15
1.12
1.09
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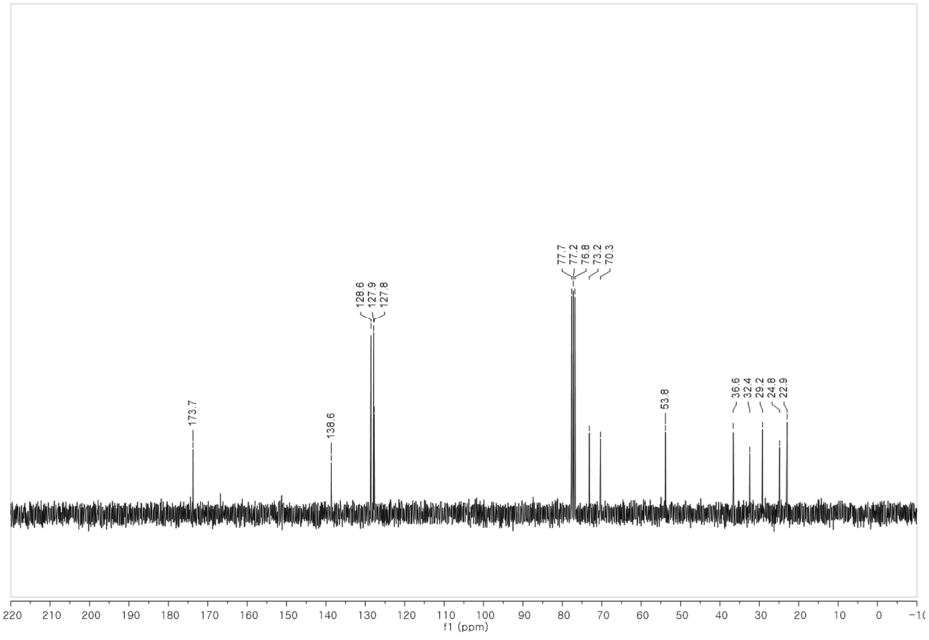
6.32
4.29
2.90
10.72
2.25
2.11
f1 (ppm)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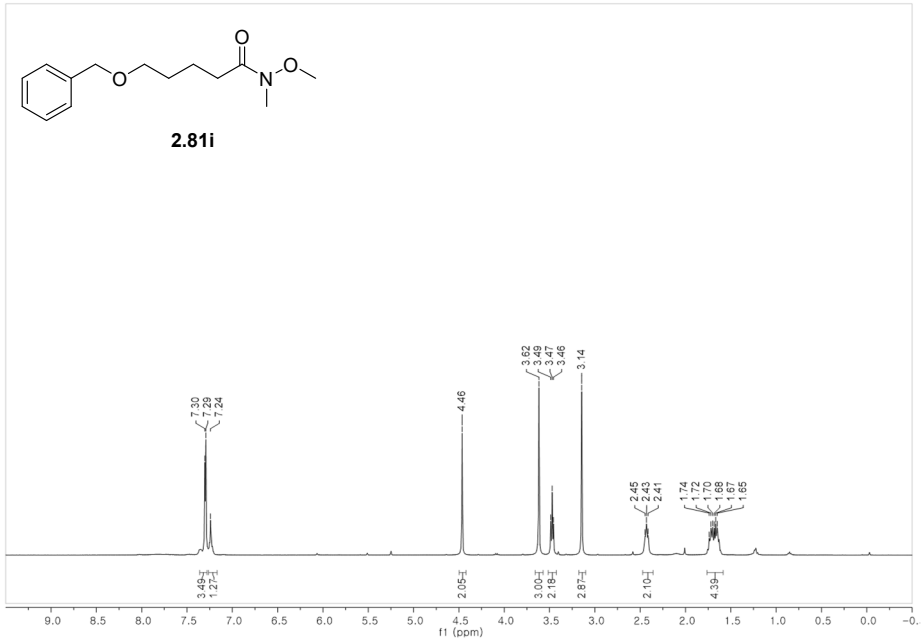
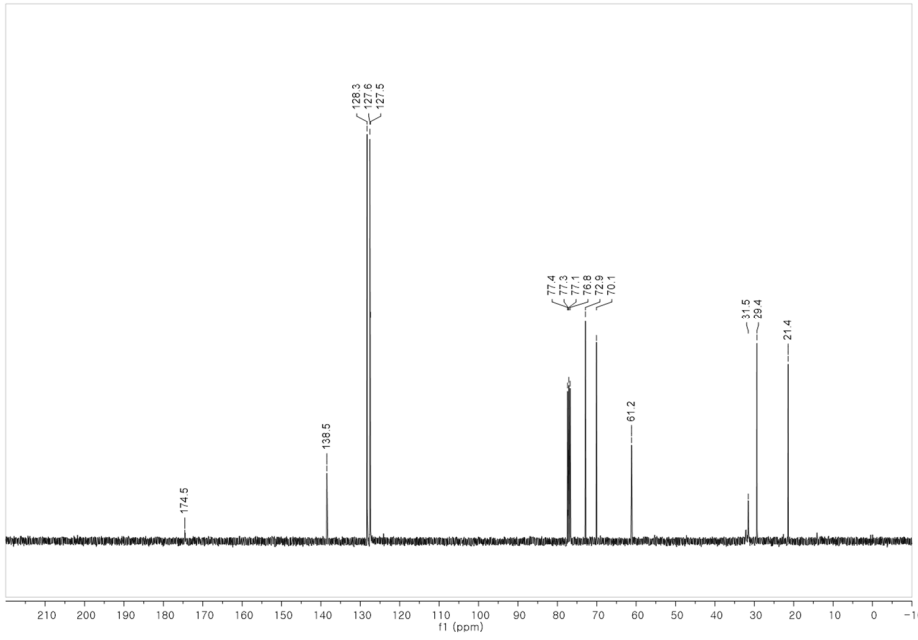
138.6
128.6
127.9
127.8
77.7
77.2
76.8
73.2
70.3
53.8
36.6
32.4
29.2
24.8
22.9
f1 (ppm)


O
O
N
O
7.30
7.29
7.24
4.46
3.62
3.49
3.47
3.46
3.14
2.45
2.43
2.41
1.74
1.72
1.70
1.68
1.67
1.65
3.49
1.27
2.05
3.00
2.18
2.87
2.10
4.39
f1 (ppm)

2.81i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127.6
127.5
77.4
77.3
77.1
76.8
72.9
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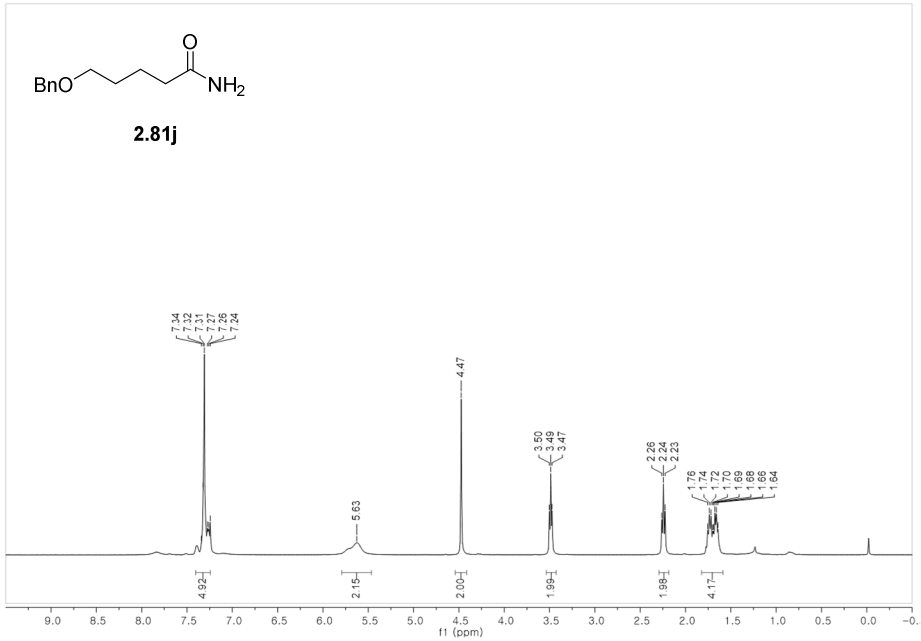
31.5
29.4
21.4
61.2
138.5
174.5
f1 (ppm)


BnO
O
NH2
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7.32
7.31
7.27
7.26
7.24
4.47
5.63
3.50
3.49
3.47
2.26
2.24
2.23
1.76
1.74
1.72
1.70
1.69
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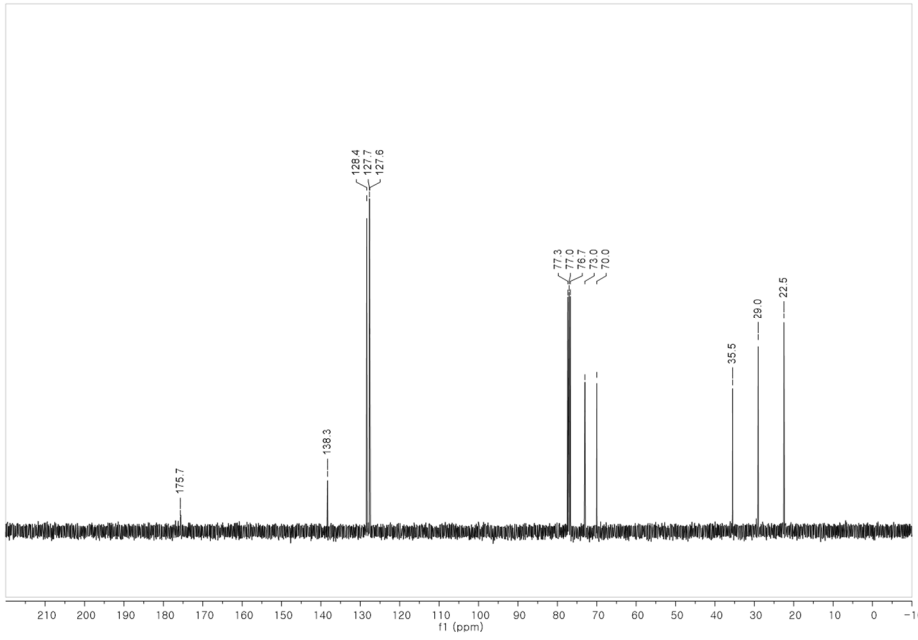
1.66
1.64
4.92
2.15
2.00
1.99
1.98
4.17
f1 (ppm)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127.7
127.6
77.3
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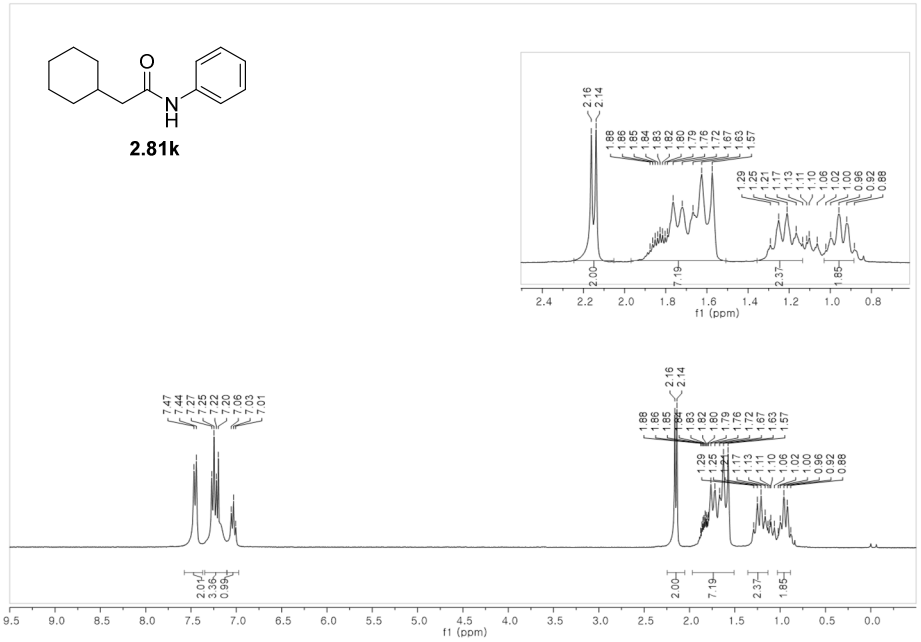
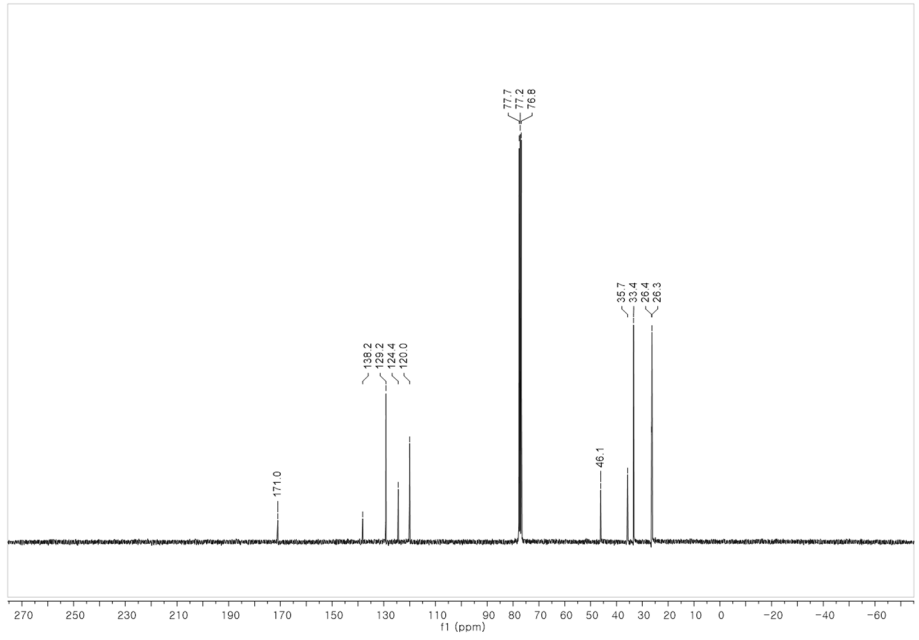
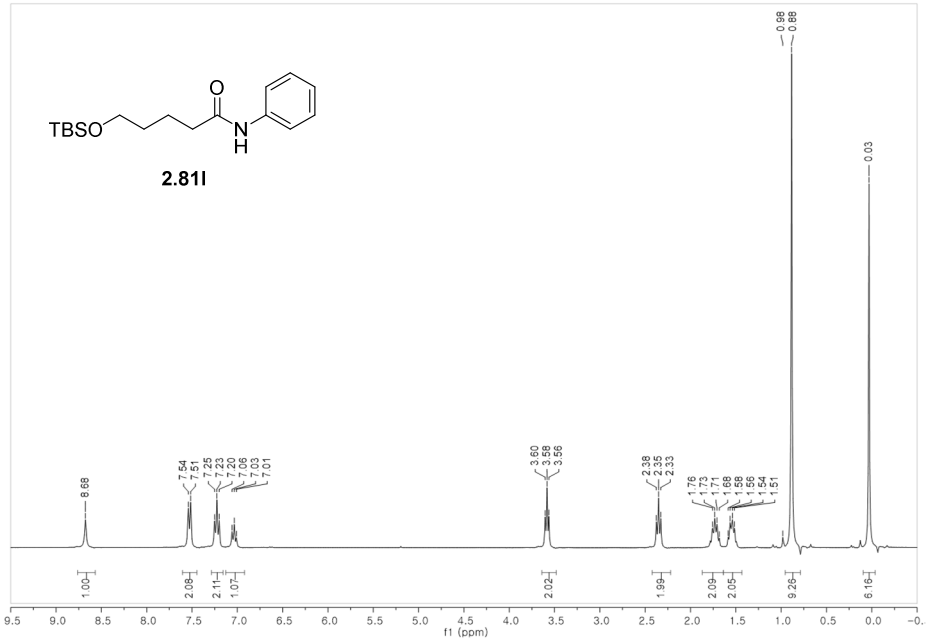
76.7
73.0
70.0
35.5
29.0
22.5
175.7
138.3
f1 (ppm)


O
N
H
2.81k
f1 (ppm)


77.7
77.2
76.8
35.7
33.4
26.4
26.3
138.2
129.2
124.4
120.0
171.0
46.1
f1 (ppm)


TBSO
O
N
H
2.81l
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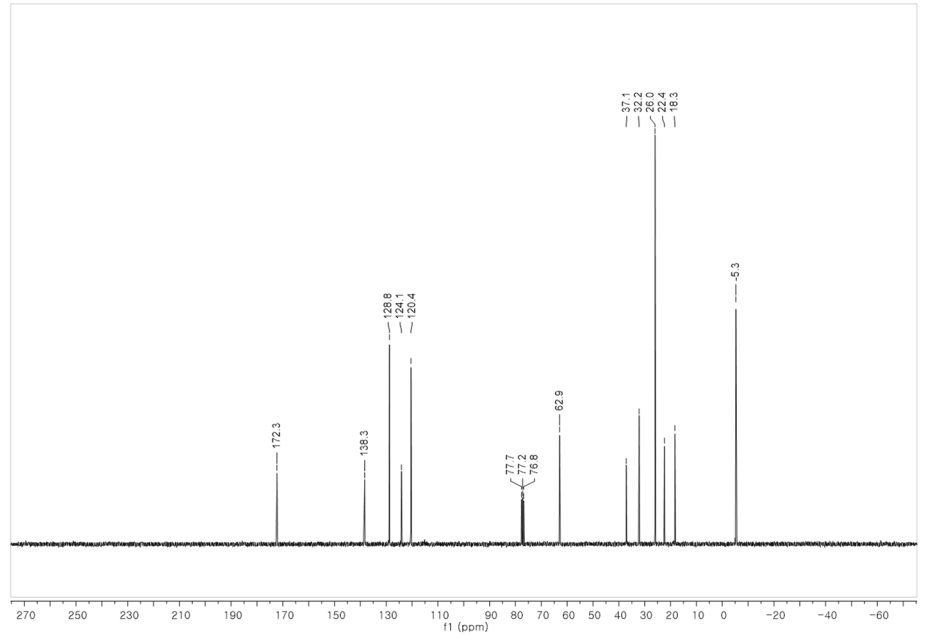
0.88
0.03
8.68
7.54
7.51
7.25
7.23
7.20
7.06
7.03
7.01
3.60
3.58
3.56
2.38
2.35
2.33
1.76
1.73
1.71
1.68
1.58
1.56
1.54
1.51
1.00
2.08
2.11
1.07
2.02
1.99
2.09
2.05
9.26
6.16
f1 (ppm)


37.1
32.2
26.0
22.4
18.3
-5.3
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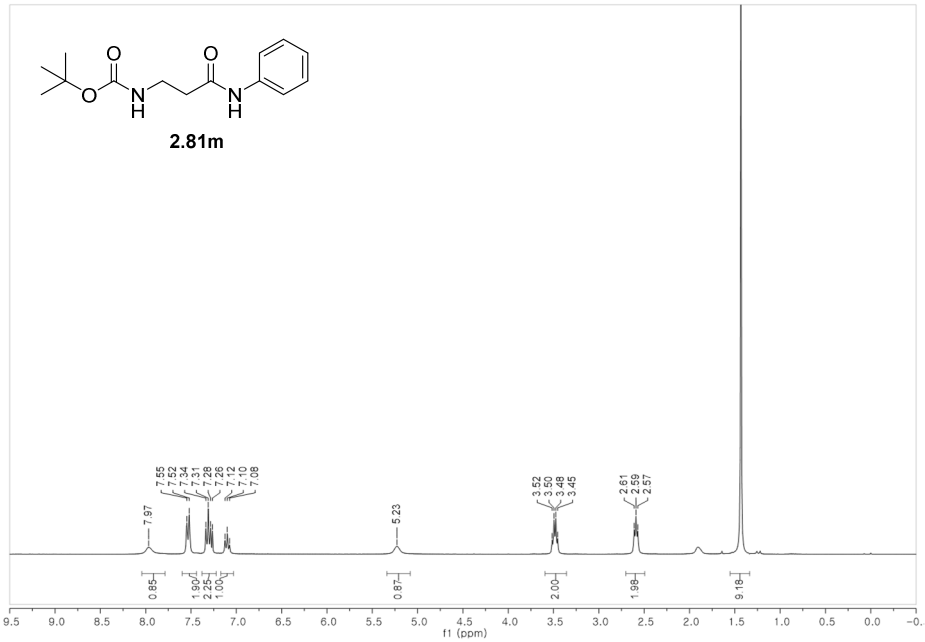
124.1
120.4
172.3
138.3
77.7
77.2
76.8
62.9
f1 (ppm)


2.81m
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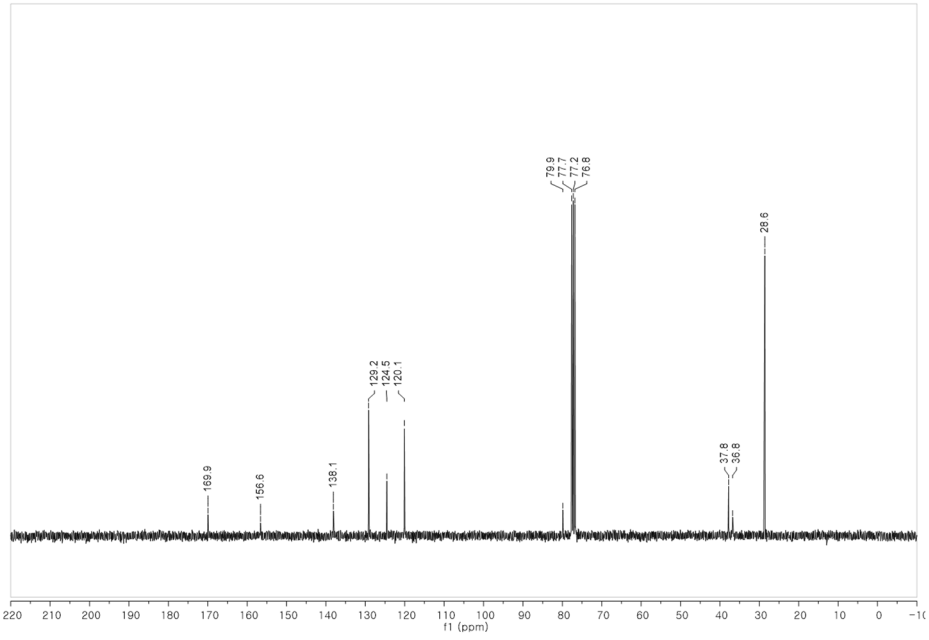
7.31
7.28
7.26
7.12
7.10
7.08
5.23
3.52
3.50
3.48
3.46
2.61
2.59
2.57
0.85
1.90
2.25
1.00
0.87
2.00
1.98
9.18
f1 (ppm)


169.9
156.6
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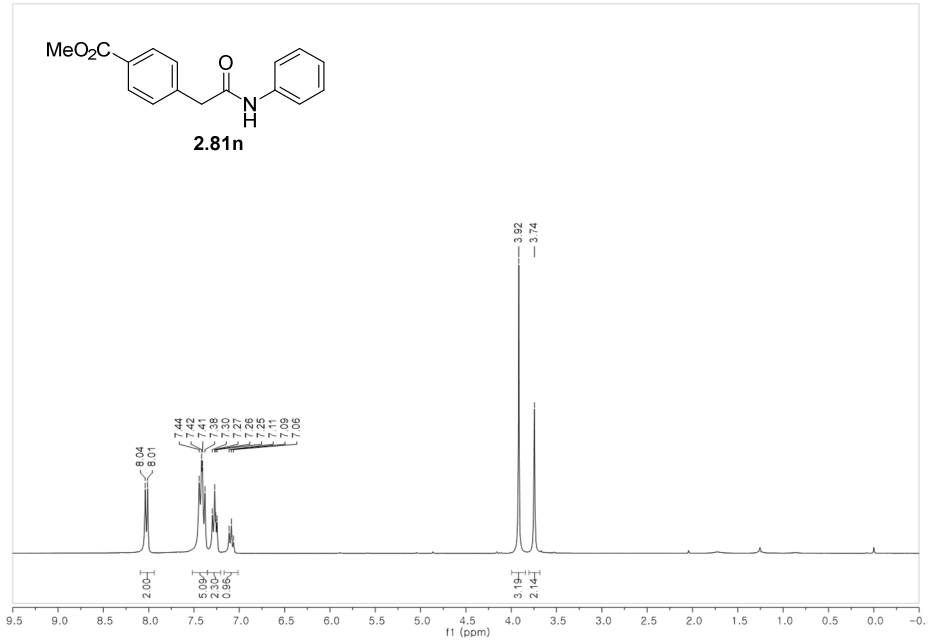
129.2
124.5
120.1
79.9
77.7
77.2
76.8
37.8
36.8
28.6
f1 (ppm)


MeO2C
O
N
H
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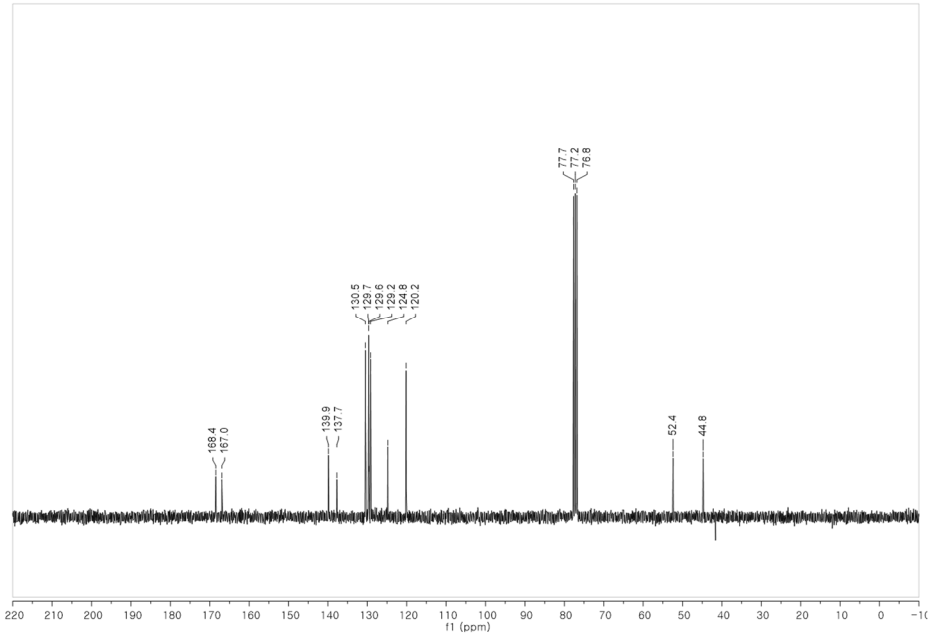
8.04
8.01
7.44
7.42
7.41
7.38
7.30
7.27
7.26
7.25
7.11
7.09
7.06
3.92
3.74
2.00
5.09
2.20
0.95
3.19
2.14
f1 (ppm)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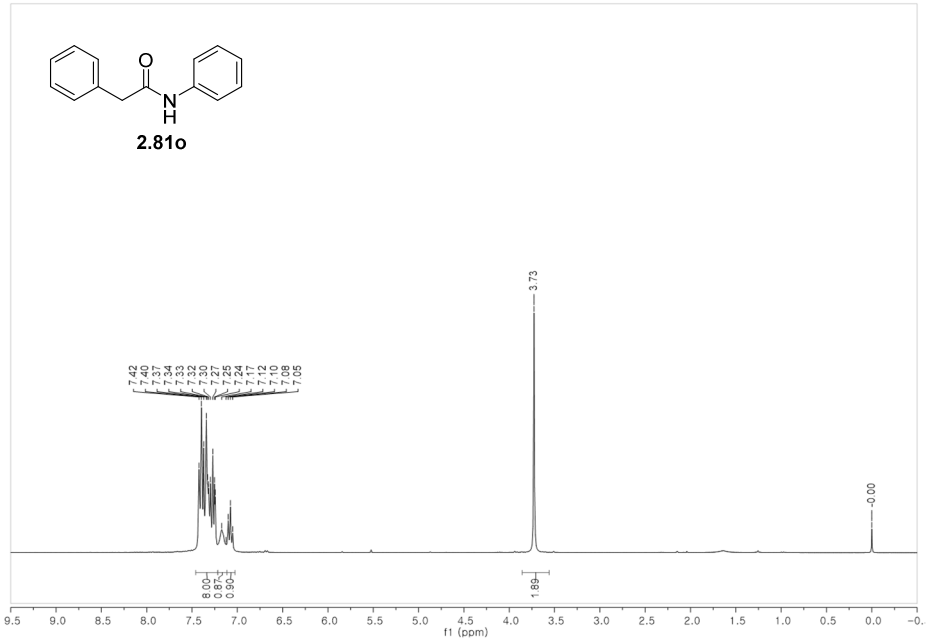
167.0
139.9
137.7
130.5
129.7
129.6
129.2
124.8
120.2
77.7
77.2
76.8
52.4
44.8
f1 (ppm)


2.81o
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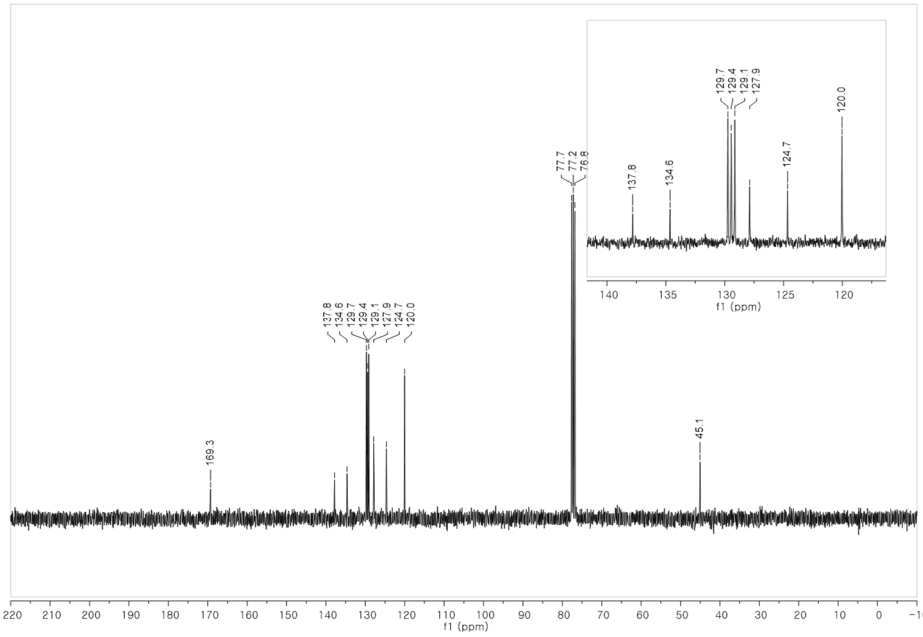
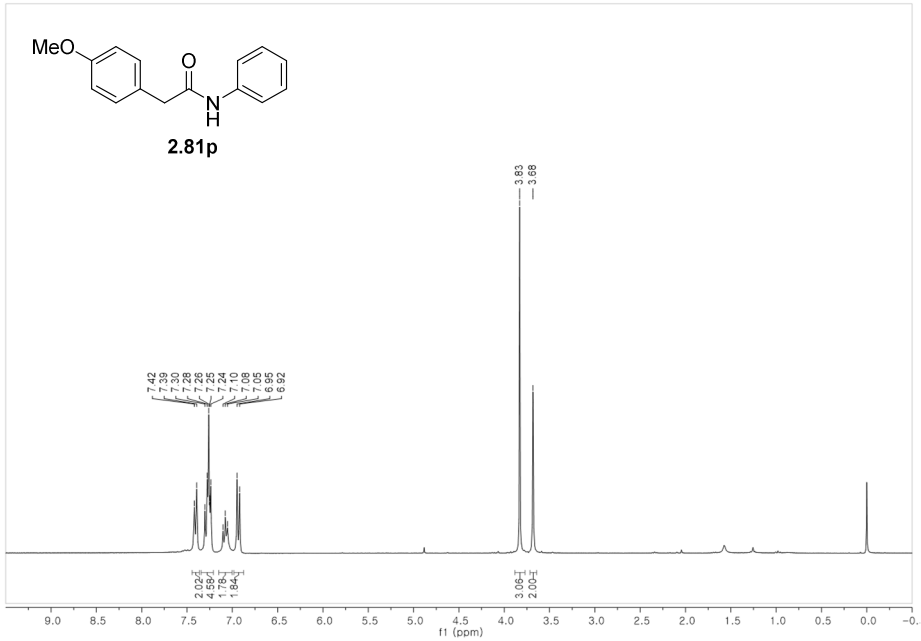
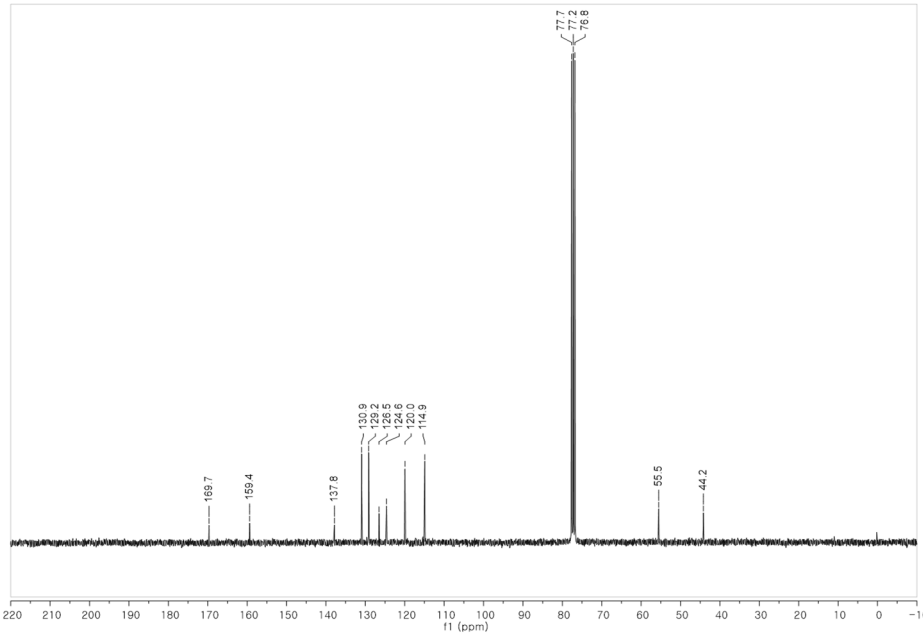
7.40
7.37
7.34
7.33
7.32
7.30
7.27
7.25
7.24
7.17
7.12
7.10
7.08
7.05
3.73
0.00
8.00
0.87
0.90
1.89
f1 (ppm)


137.8
134.6
129.7
129.4
129.1
127.9
124.7
120.0
77.7
77.2
76.8
169.3
45.1
f1 (ppm)


MeO
O
N
H
2.81p
3.83
3.68
7.42
7.39
7.30
7.28
7.26
7.25
7.24
7.10
7.08
7.05
6.95
6.92
2.02
4.59
1.78
1.84
3.06
2.00
f1 (ppm)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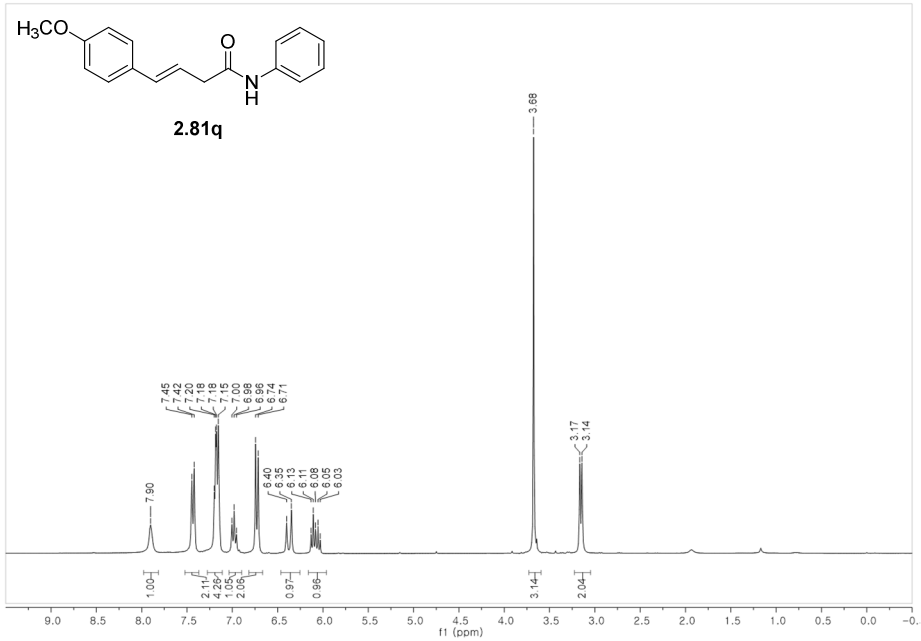
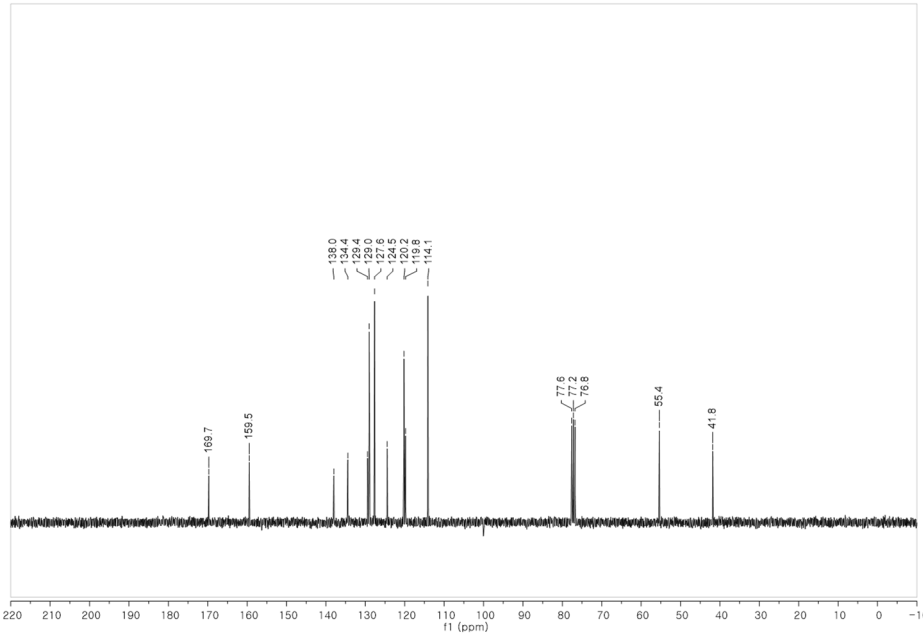
77.2
76.8
130.9
129.2
126.5
124.6
120.0
114.9
169.7
159.4
137.8
55.5
44.2
f1 (ppm)


H3CO
O
N
H
2.81q
3.68
7.45
7.42
7.20
7.18
7.18
7.15
7.00
6.98
6.96
6.74
6.71
7.90
6.40
6.35
6.13
6.11
6.08
6.05
6.03
3.17
3.14
1.00
2.11
4.26
1.05
2.06
0.97
0.96
3.14
2.04
f1 (ppm)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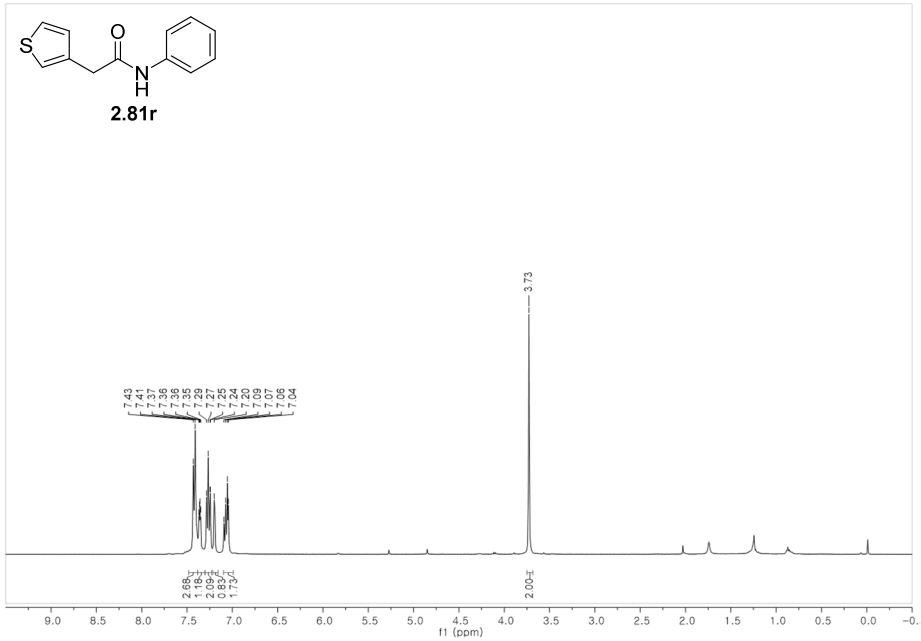
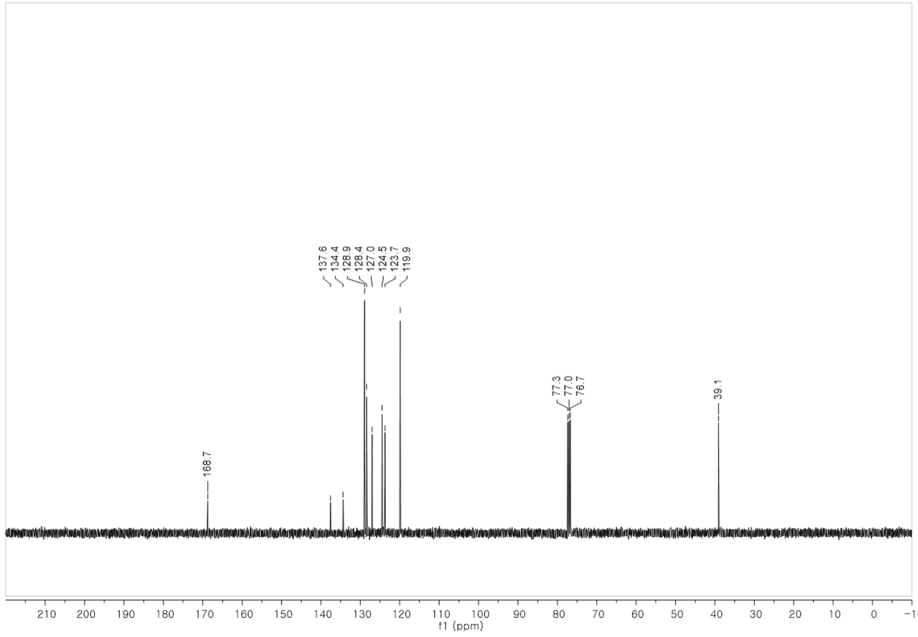
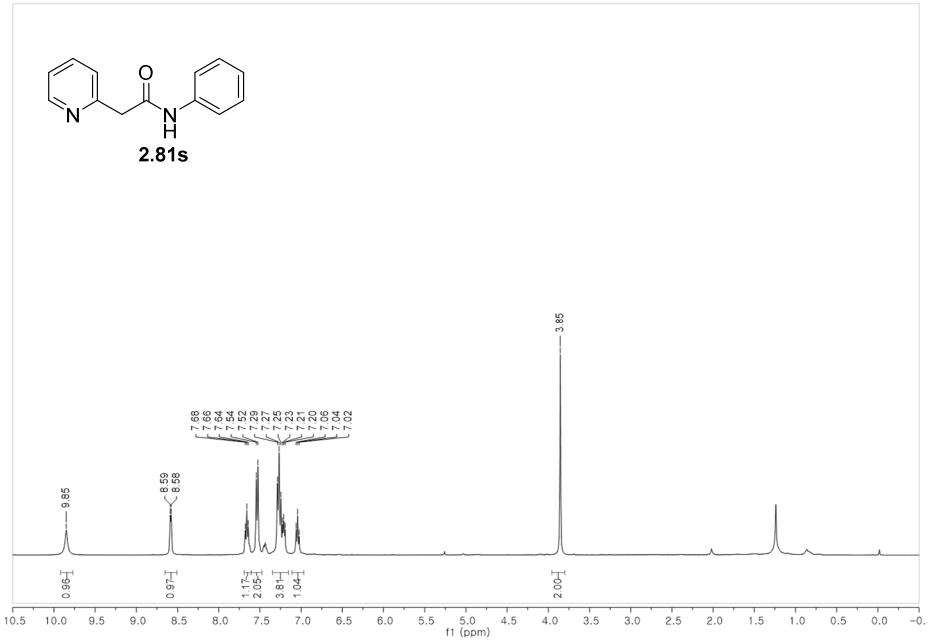
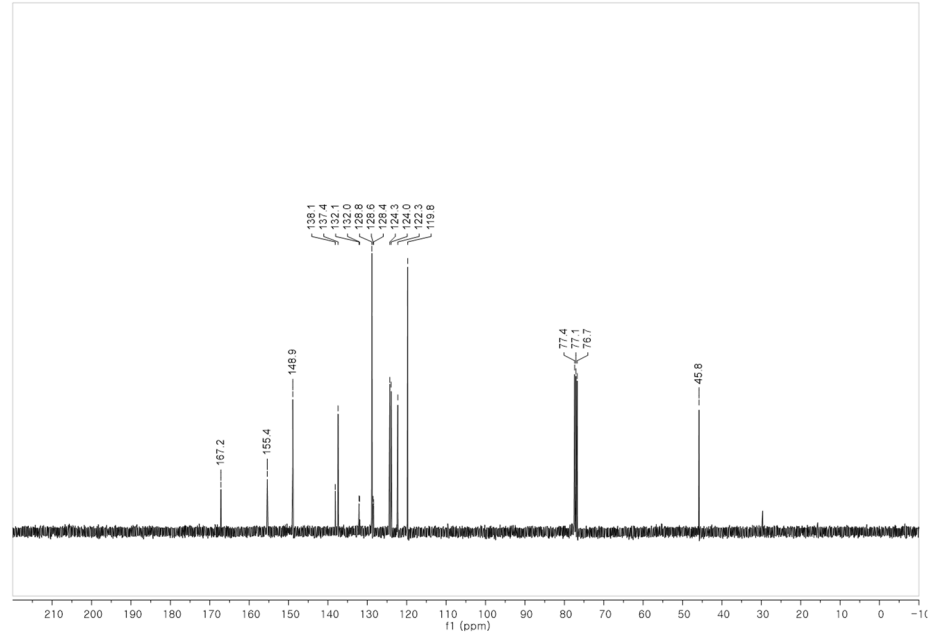
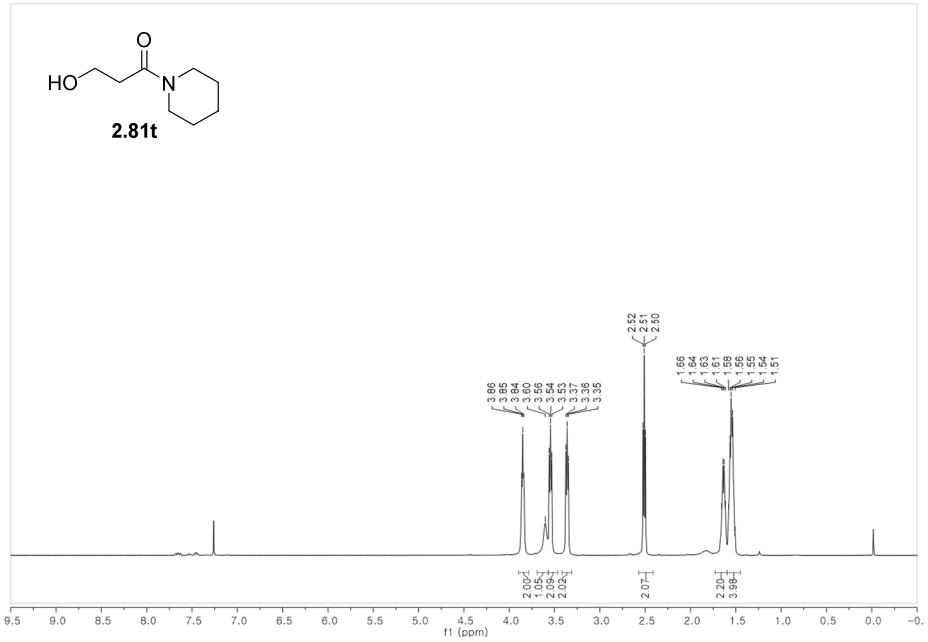
134.4
129.4
129.0
127.6
124.5
120.2
119.8
114.1
77.6
77.2
76.8
55.4
41.8
169.7
159.5
f1 (ppm)


S
O
N
H
2.81r
7.43
7.41
7.37
7.36
7.36
7.35
7.29
7.27
7.25
7.24
7.20
7.09
7.07
7.06
7.04
3.73
2.68
1.18
2.09
0.83
1.13
2.00
f1 (ppm)


137.6
134.4
128.9
128.4
127.0
124.5
123.7
119.9
77.3
77.0
76.7
39.1
168.7
f1 (ppm)


2.81s
9.85
8.59
8.58
7.68
7.66
7.64
7.54
7.52
7.29
7.27
7.25
7.23
7.21
7.20
7.06
7.04
7.02
3.85
0.96
0.97
1.17
2.05
3.81
1.04
2.00
f1 (ppm)


167.2
155.4
148.9
138.1
133.4
132.1
132.0
128.8
128.6
128.4
124.3
124.0
122.3
119.8
77.4
77.1
76.7
45.8
f1 (ppm)


HO
O
N
2.81t
3.86
3.85
3.84
3.60
3.56
3.54
3.53
3.37
3.36
3.35
2.52
2.51
2.50
1.66
1.64
1.63
1.61
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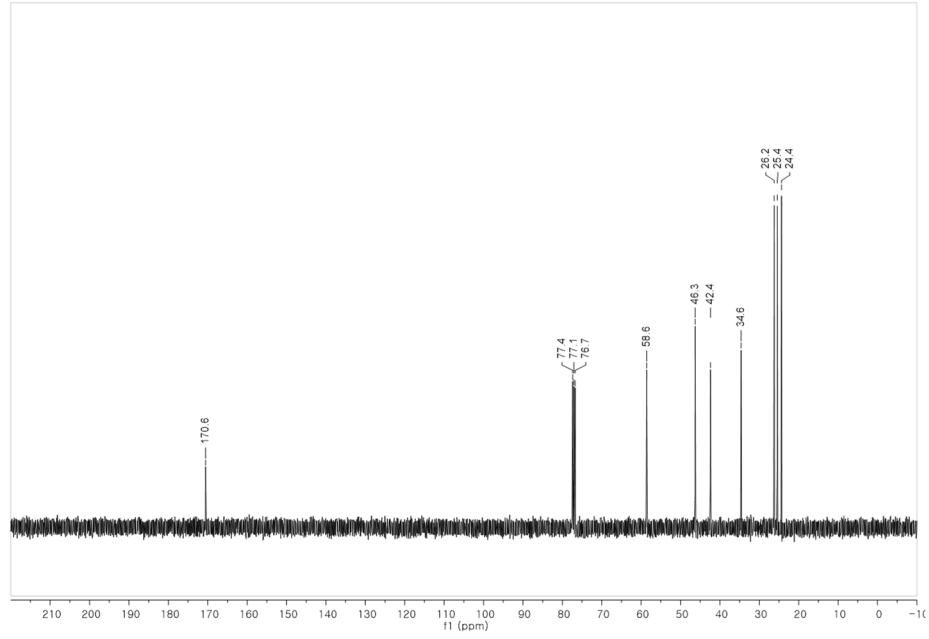
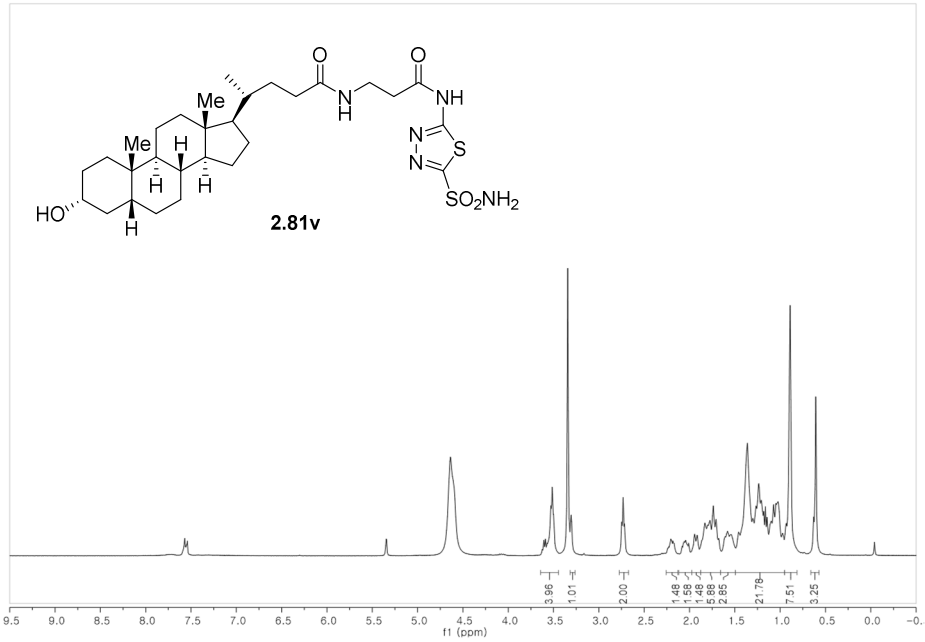
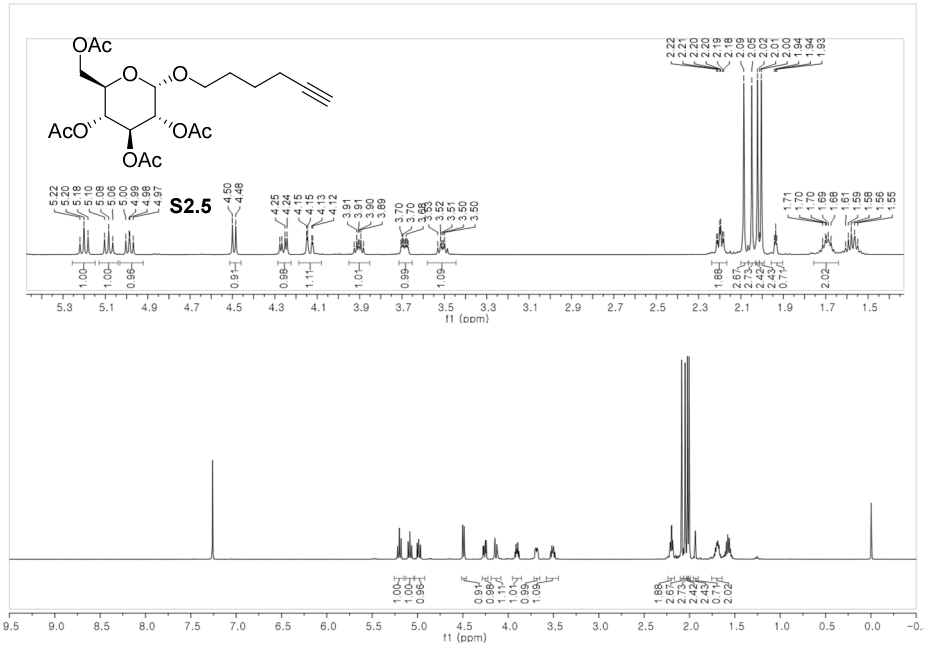
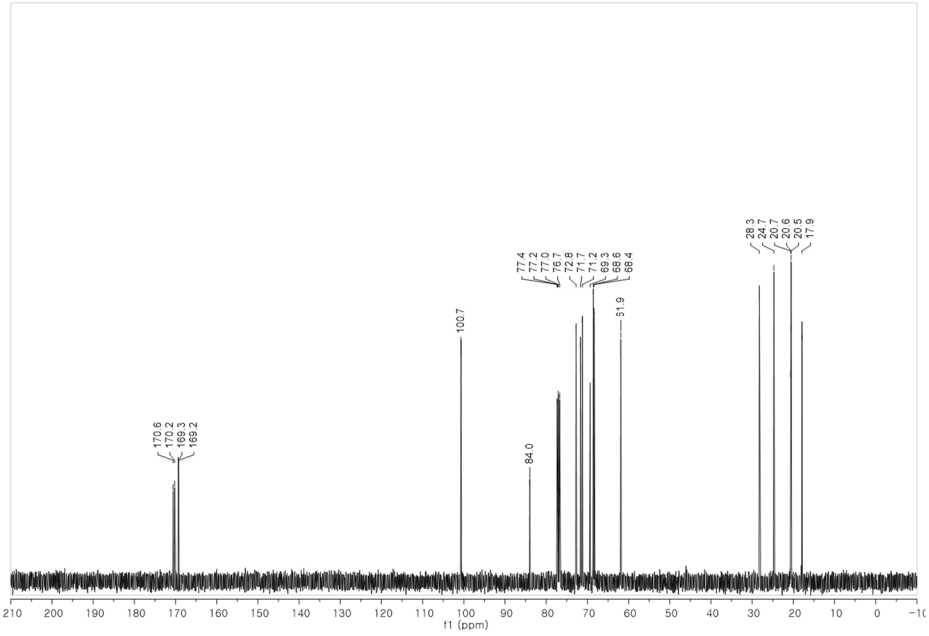
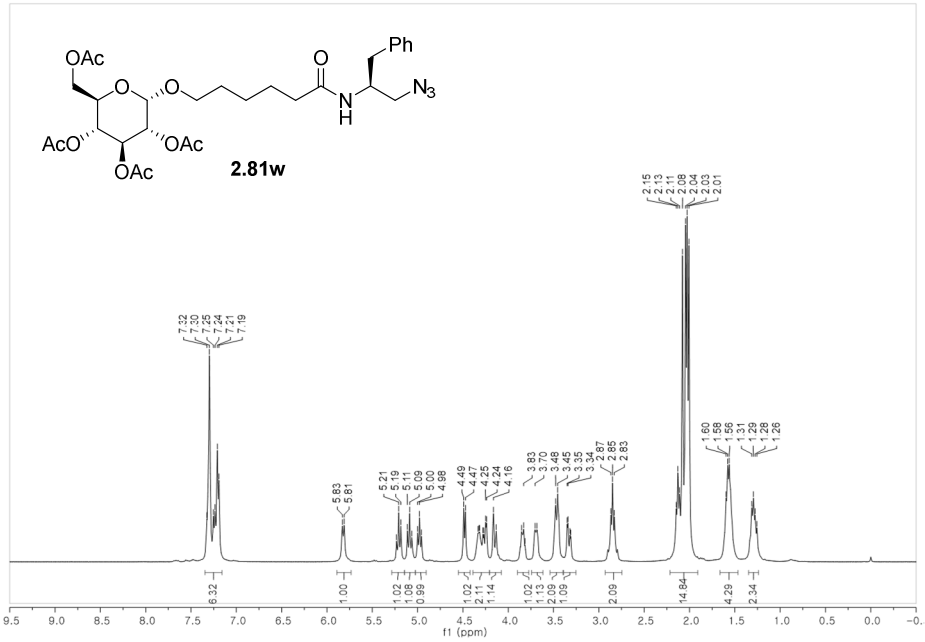
2.02
2.07
2.20
3.98
f1 (ppm)

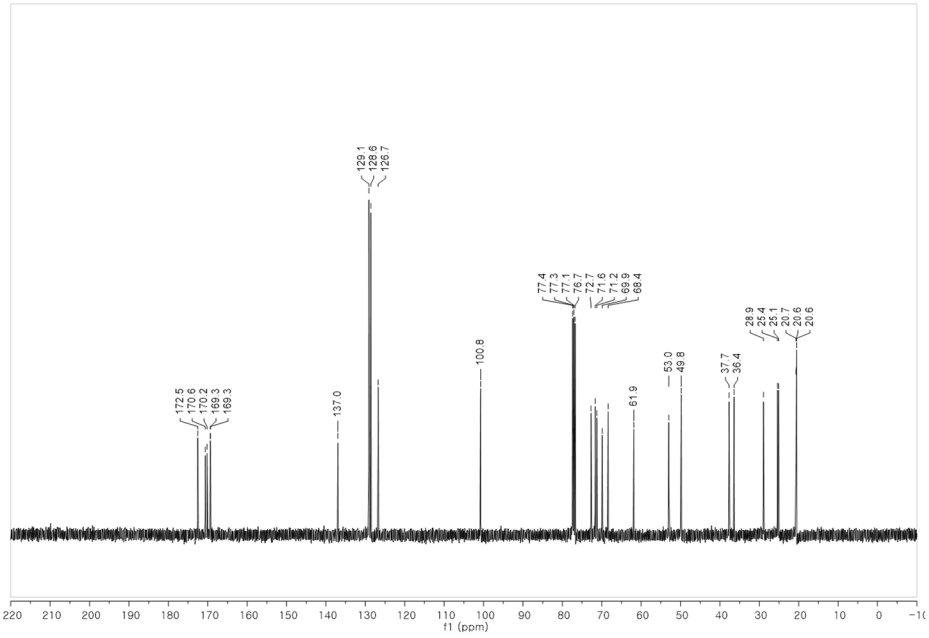

170.6
77.4
77.1
76.7
58.6
46.3
42.4
34.6
26.2
25.4
24.4
f1 (ppm)

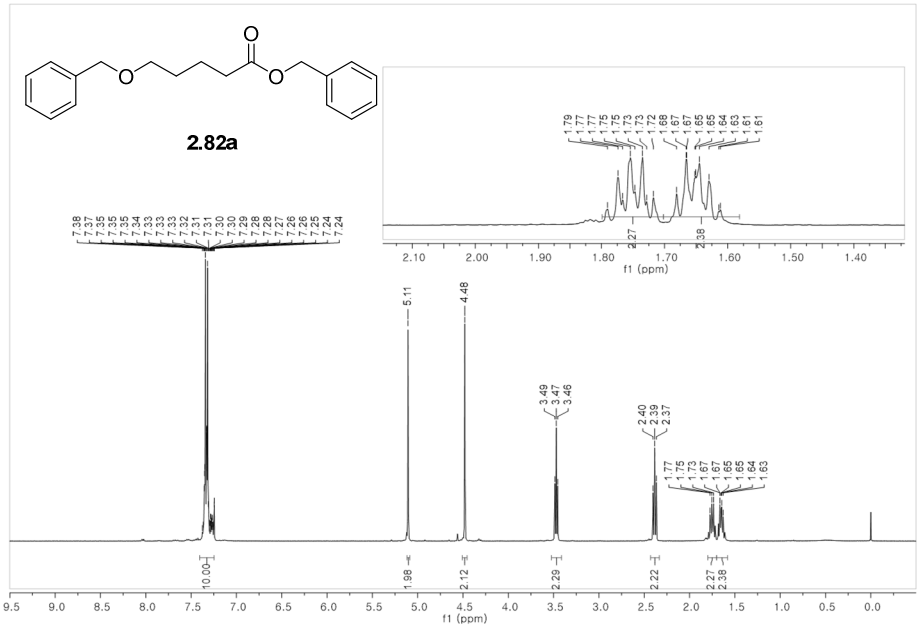

O
O
N
H
NH
N
N
S
SO2NH2
Me
Me
H
H
H
HO
H
2.81v
3.96
1.01
2.00
1.48
1.58
1.48
5.68
2.85
21.78
7.51
3.25
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

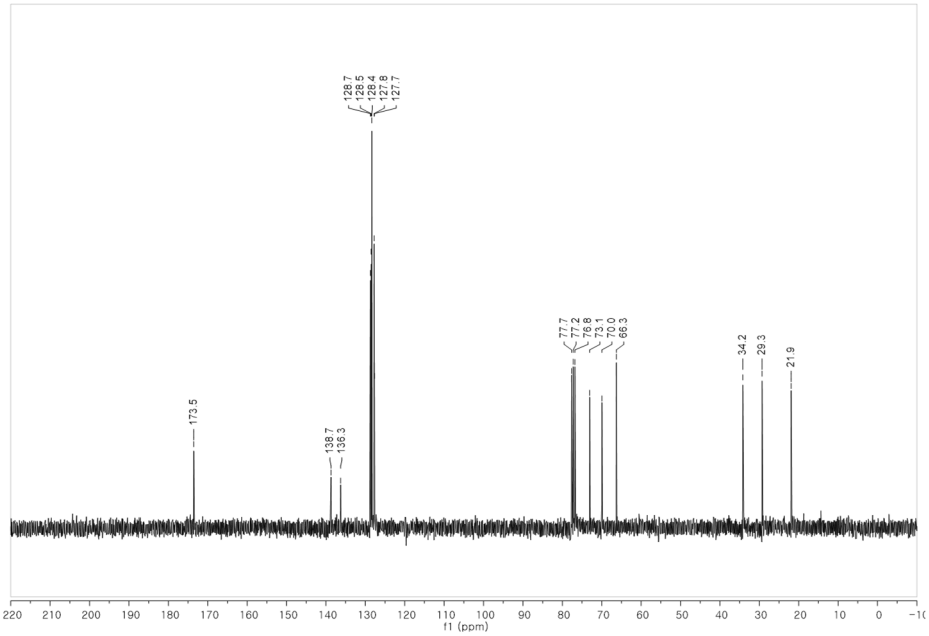

OAc
AcO
OAc
OAc
O
O
S2.5
f1 (ppm)

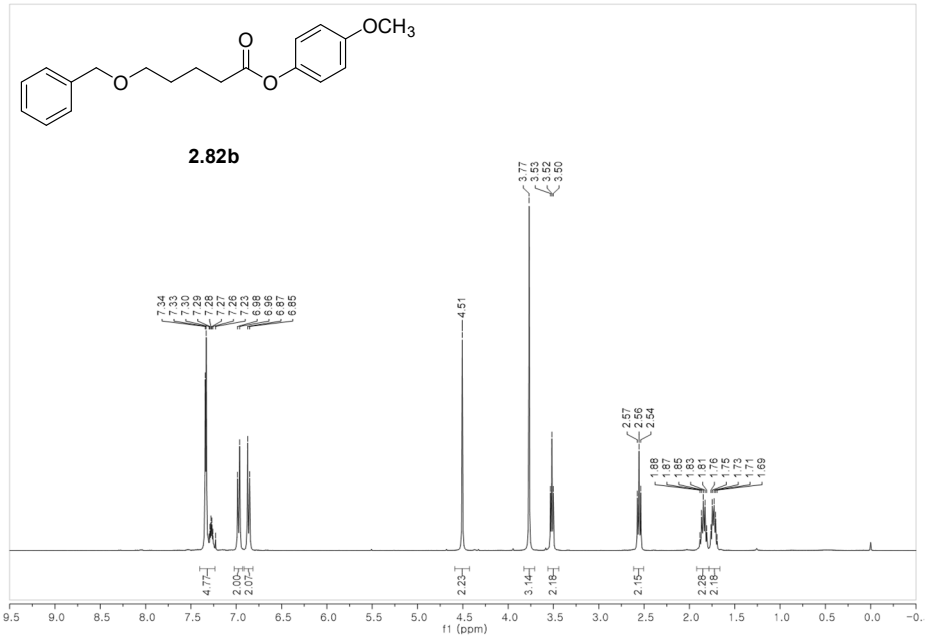

f1 (ppm)


OAc
OAc
AcO
OAc
O
O
O
N
H
Ph
N3
2.81w
7.32
7.30
7.25
7.24
7.21
7.19
5.83
5.81
5.21
5.19
5.11
5.09
5.00
4.98
4.49
4.47
4.25
4.24
4.16
3.83
3.70
3.48
3.45
3.35
3.34
2.87
2.85
2.83
2.15
2.13
2.11
2.08
2.04
2.03
2.01
1.60
1.58
1.56
1.31
1.29
1.28
1.26
6.32
1.00
1.02
1.08
0.99
1.02
2.11
1.14
1.02
1.13
2.09
1.09
2.09
14.84
4.29
2.34
f1 (ppm)


172.5
170.6
170.2
169.3
169.3
137.0
129.1
128.6
126.7
100.8
77.4
77.3
77.1
76.7
72.7
71.6
71.2
69.9
68.4
61.9
53.0
49.8
37.7
36.4
28.9
25.4
25.1
20.7
20.6
20.6
f1 (ppm)


2.82a
f1 (ppm)


f1 (ppm)


OCH3
O
O
O
2.82b
7.34
7.33
7.30
7.29
7.28
7.27
7.26
7.23
6.98
6.96
6.87
6.85
4.51
3.77
3.53
3.52
3.50
2.57
2.56
2.54
1.88
1.87
1.85
1.83
1.81
1.76
1.75
1.73
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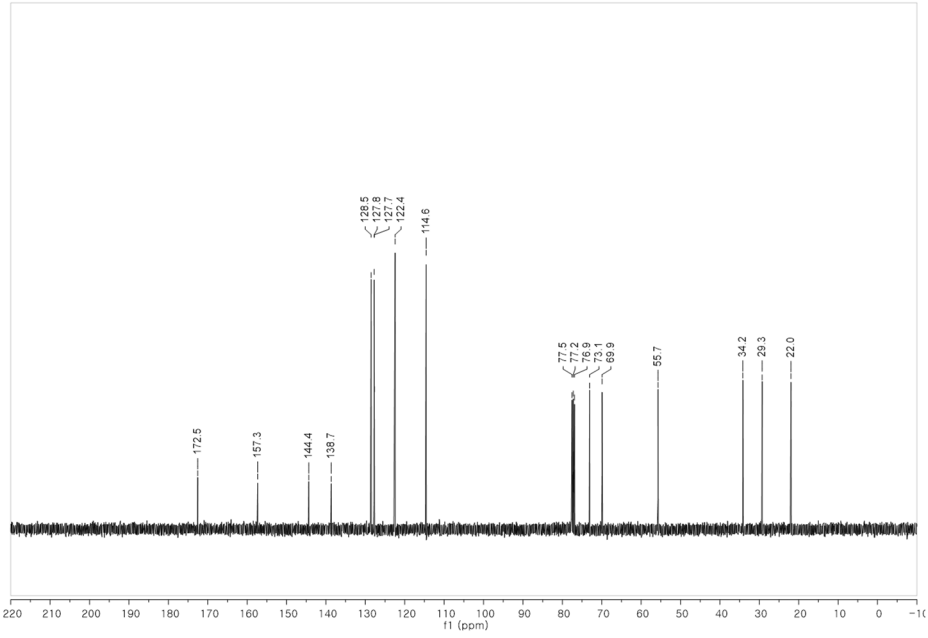
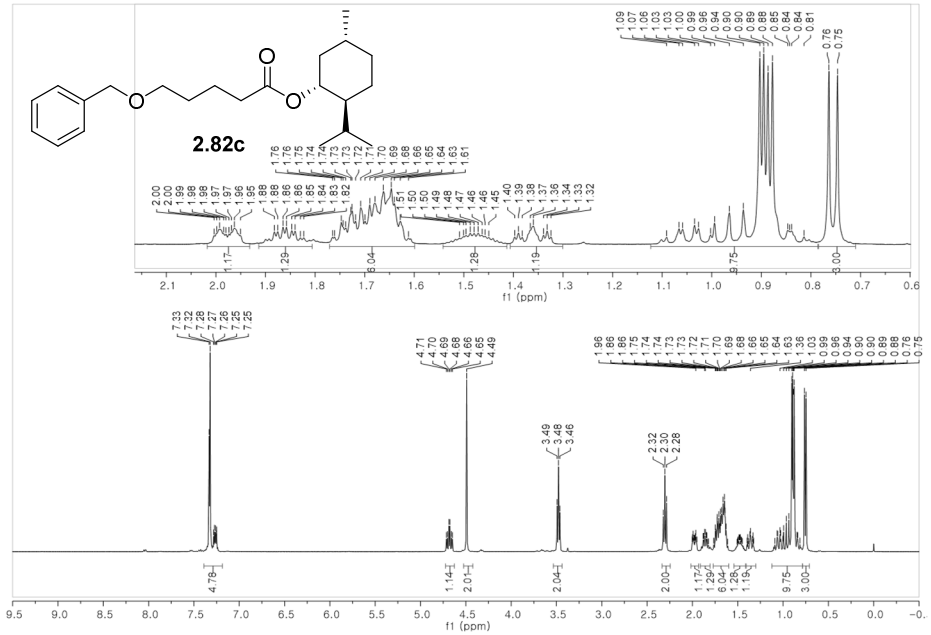
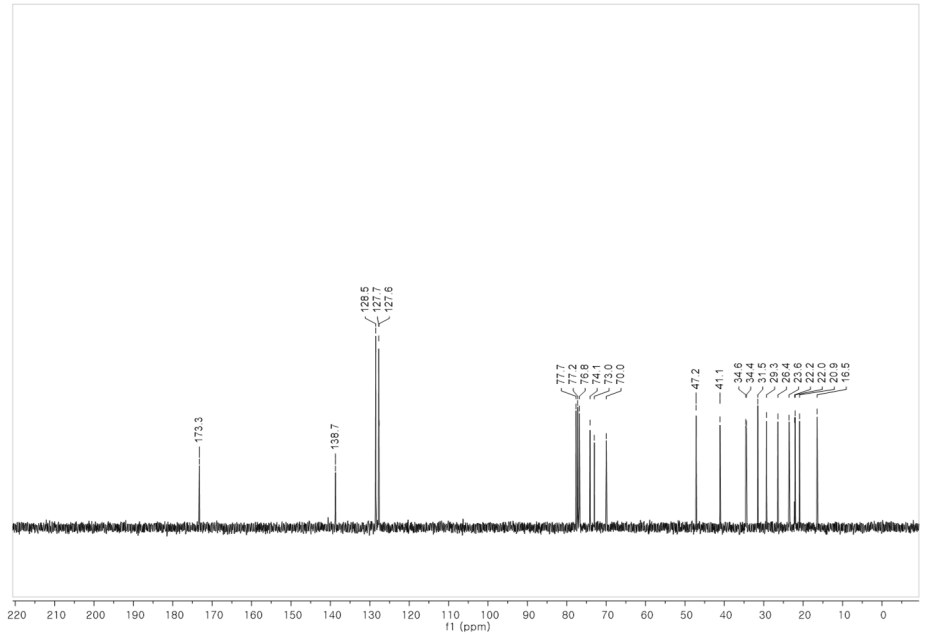
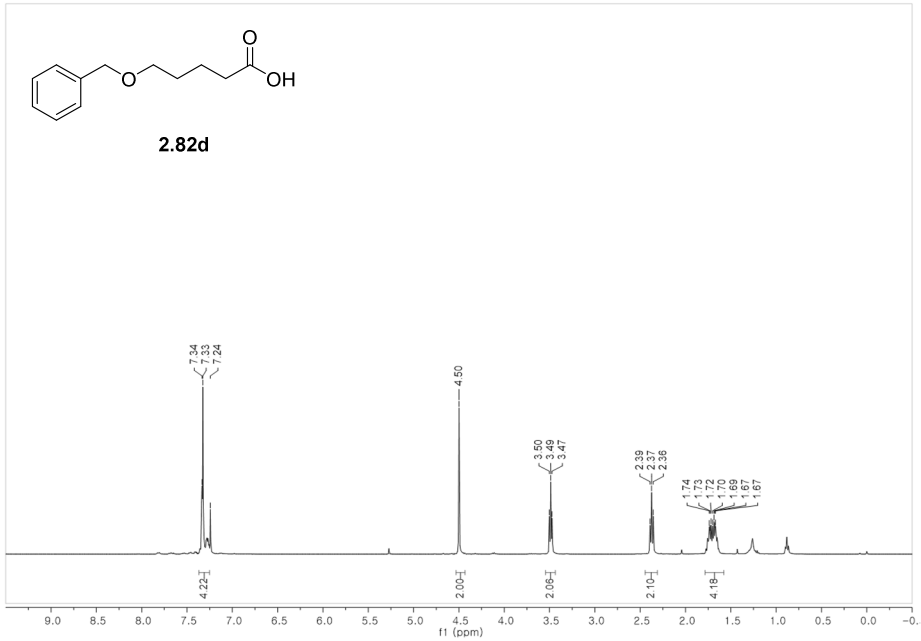
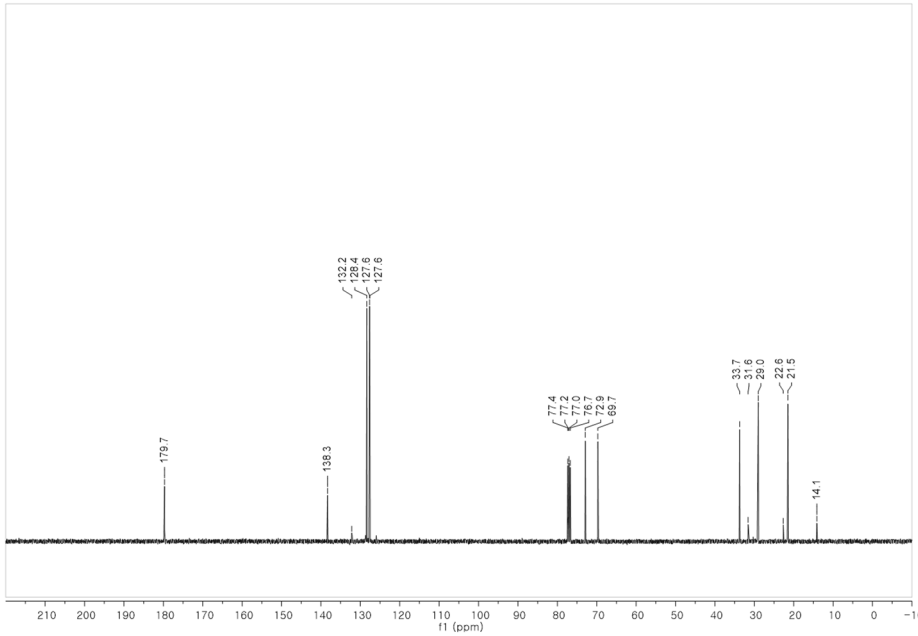
3.14
2.18
2.15
2.28
2.18
f1 (ppm)

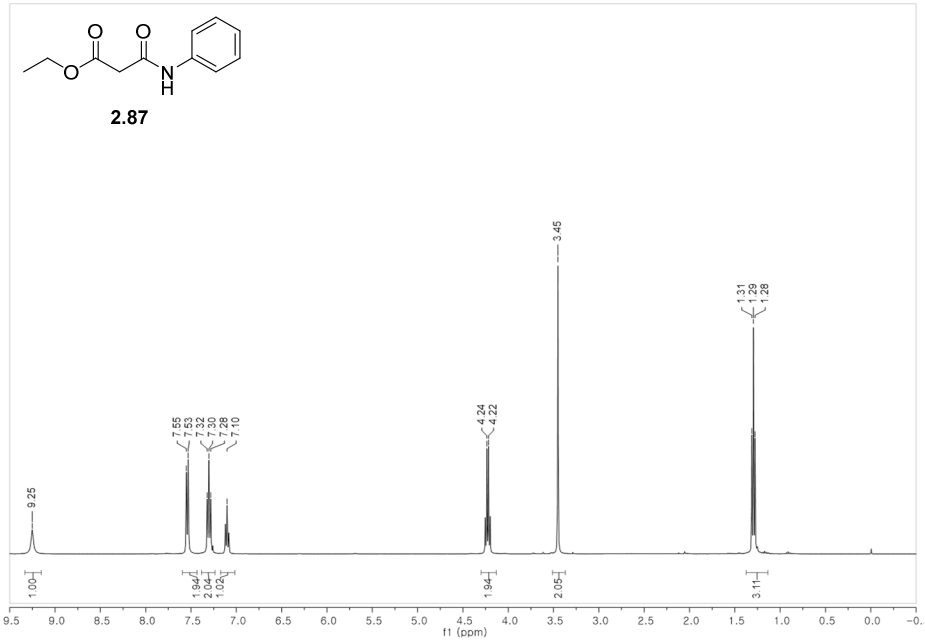

128.5
127.8
127.7
122.4
114.6
77.5
77.2
76.9
73.1
69.9
55.7
34.2
29.3
22.0
172.5
157.3
144.4
138.7
f1 (ppm)

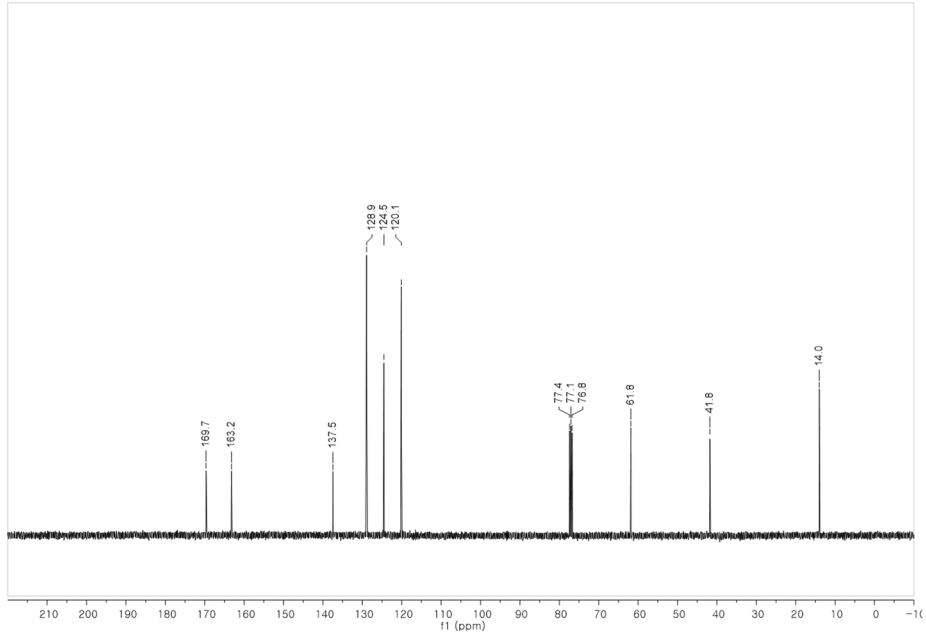

2.82c
f1 (ppm)

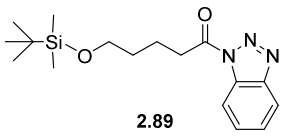

f1 (ppm)


O
O
OH
2.82d
7.34
7.33
7.24
4.50
3.50
3.49
3.47
2.39
2.37
2.36
1.74
1.73
1.72
1.70
1.69
1.67
1.67
4.22
2.00
2.06
2.10
4.18
f1 (ppm)


132.2
128.4
127.6
127.6
179.7
138.3
77.4
77.2
77.0
76.7
72.9
69.7
33.7
31.6
29.0
22.6
21.5
14.1
f1 (ppm)

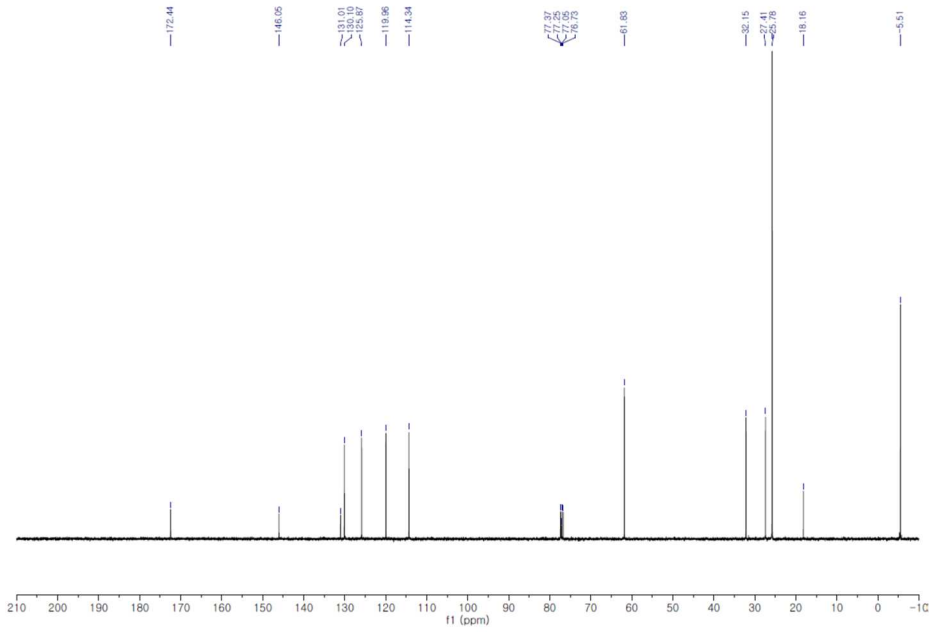

2.87
9.25
7.55
7.53
7.32
7.30
7.28
7.10
4.24
4.22
3.45
1.31
1.29
1.28
1.00
1.94
2.04
1.02
1.94
2.05
3.11
f1 (ppm)

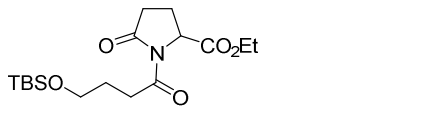

169.7
163.2
137.5
128.9
124.5
120.1
77.4
77.1
76.8
61.8
41.8
14.0
f1 (ppm)



2.89

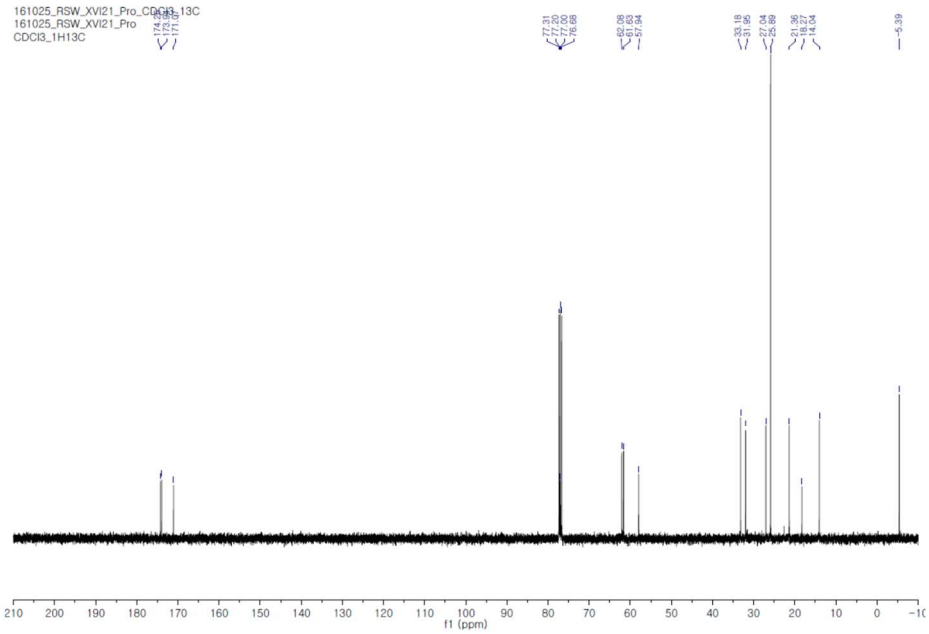
0.96
0.95
1.03
1.04
2.01
1.91
2.18
9.00
5.79
f1 (ppm)

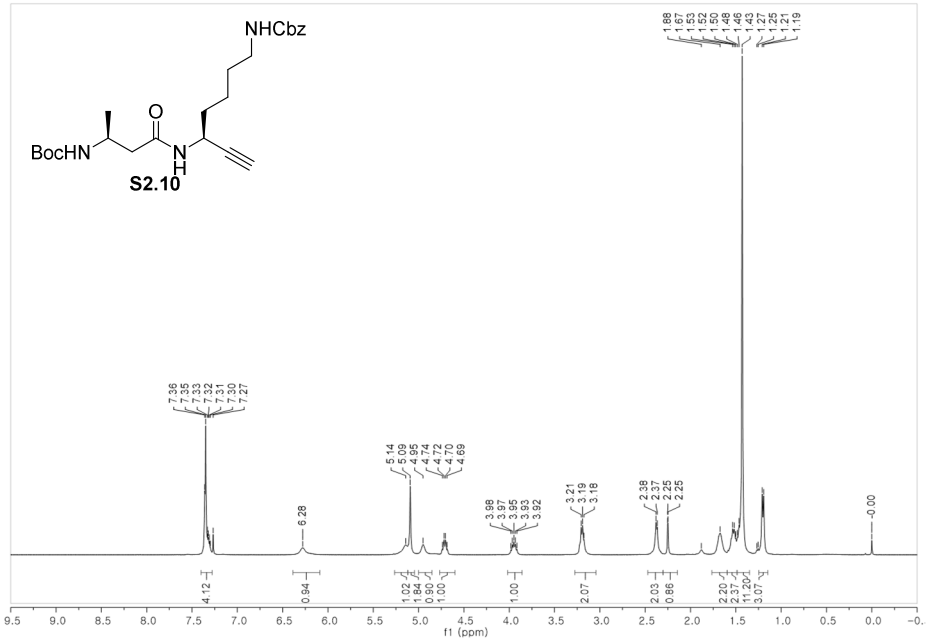

172.44
146.05
131.01
130.10
125.87
119.96
114.34
77.37
77.25
77.05
76.73
61.83
32.15
27.41
25.76
18.16
-5.51
f1 (ppm)

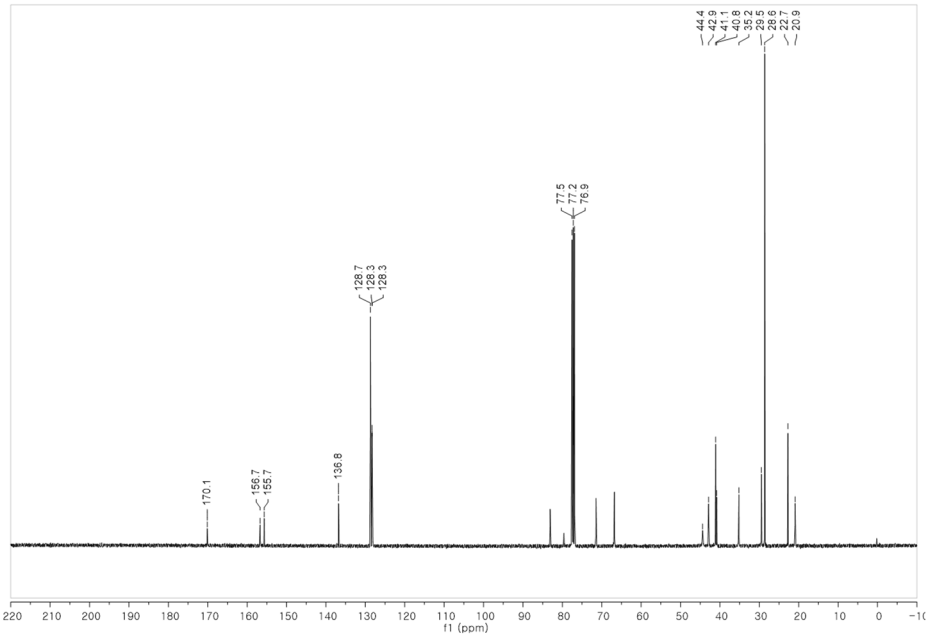

O
N
CO2Et
TBSO
O

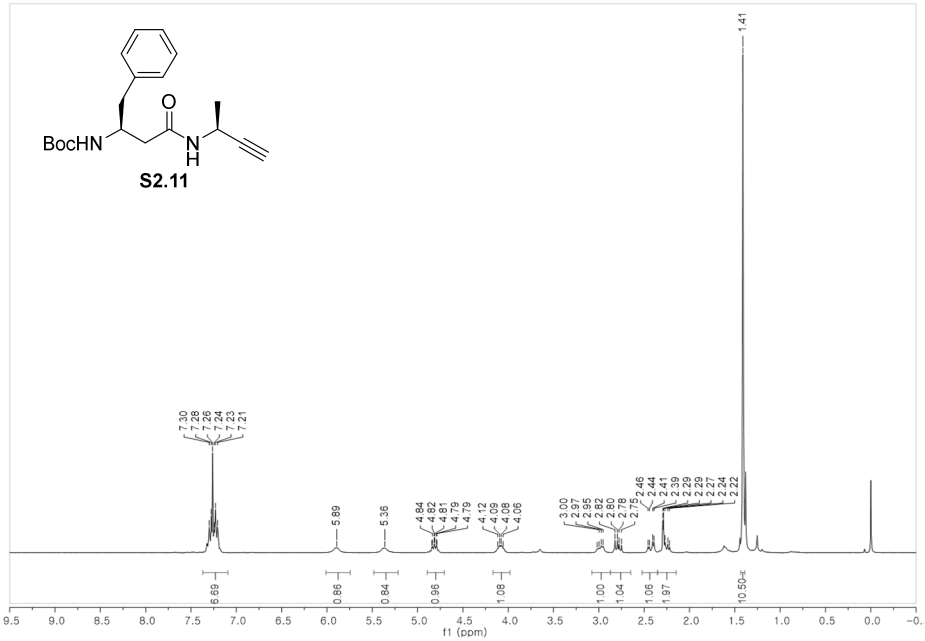
2.93

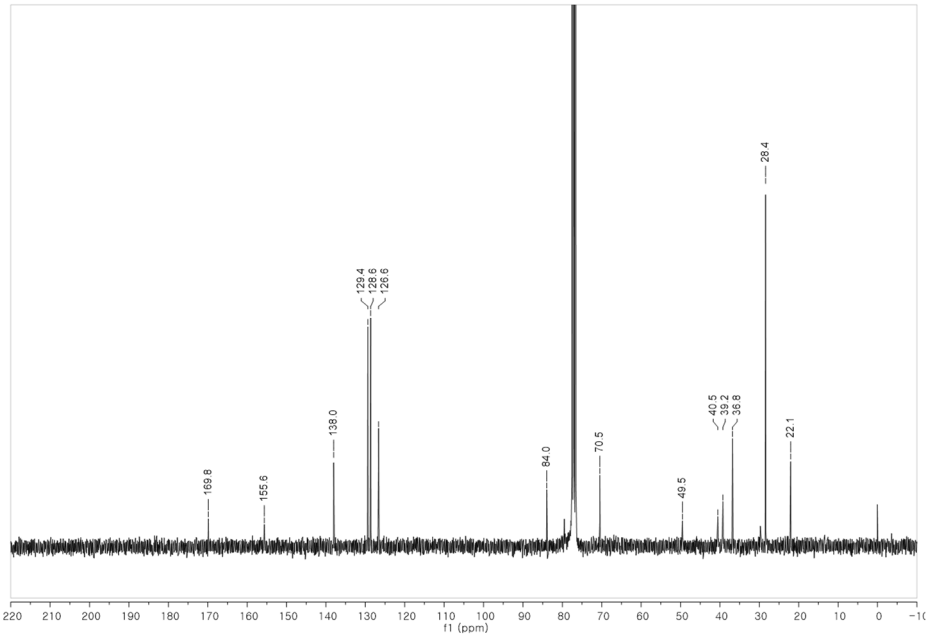
0.93
2.03
1.90
1.69
1.13
1.21
1.32
1.19
1.81
3.59
9.00
5.11
f1 (ppm)

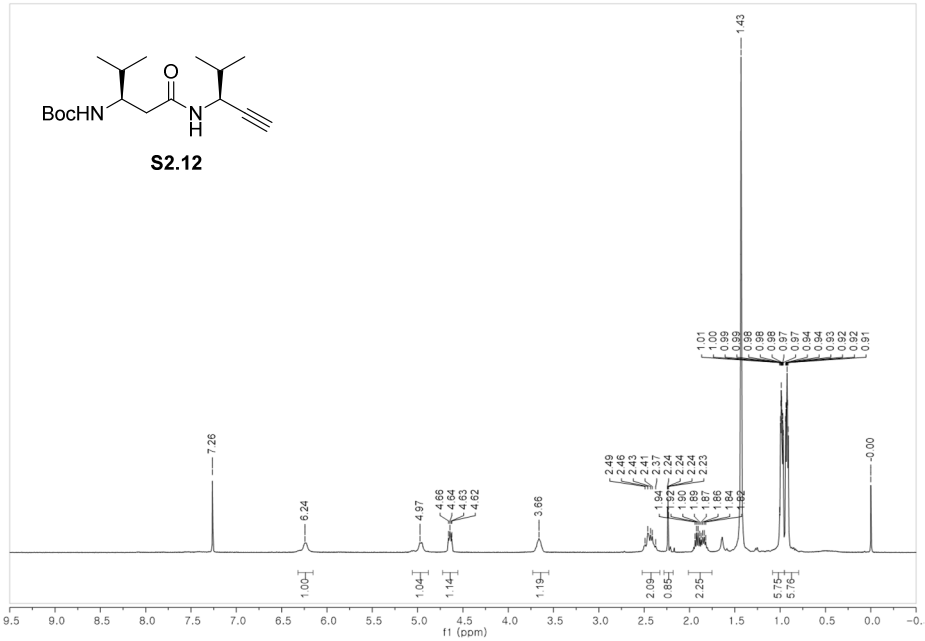

161025_RSW_XVI21_Pro_CDCl3_13C
161025_RSW_XVI21_Pro
CDCl3_1H13C
174.15
170.97
171.07
77.31
77.20
77.00
76.68
62.09
61.63
57.94
33.18
31.95
27.04
25.89
21.36
18.27
14.04
-5.39
f1 (ppm)

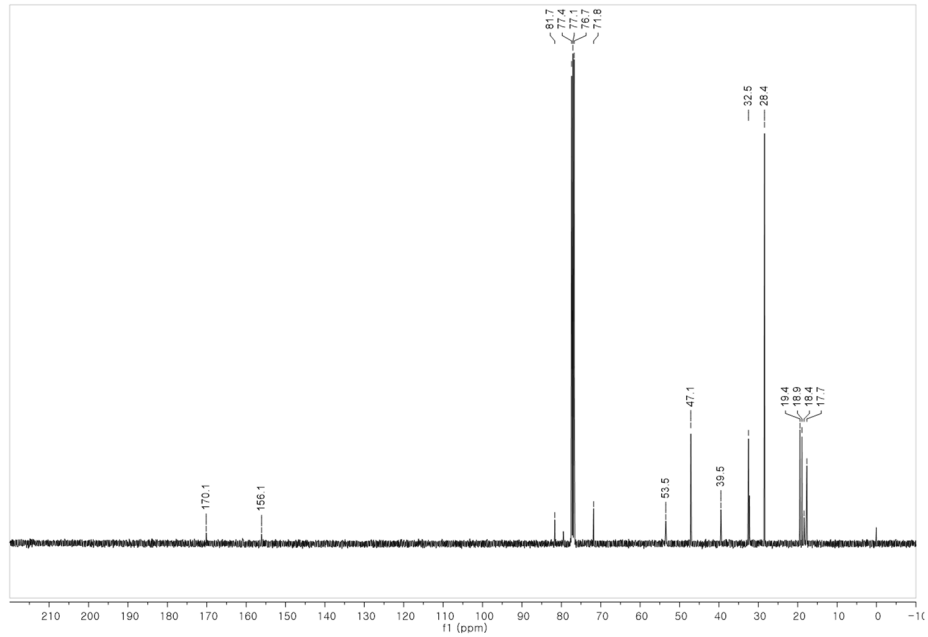

NHCbz
O
BocHN
N
H
S2.10
1.88
1.67
1.53
1.52
1.50
1.49
1.46
1.43
1.27
1.25
1.21
1.19
7.36
7.35
7.33
7.32
7.31
7.30
7.27
6.28
5.14
5.09
4.95
4.74
4.72
4.70
4.69
3.98
3.97
3.95
3.93
3.92
3.21
3.19
3.18
2.38
2.37
2.25
2.25
0.00
4.12
0.94
1.03
1.84
0.90
1.00
1.00
2.07
2.03
0.86
2.20
2.37
11.20
3.07
f1 (ppm)

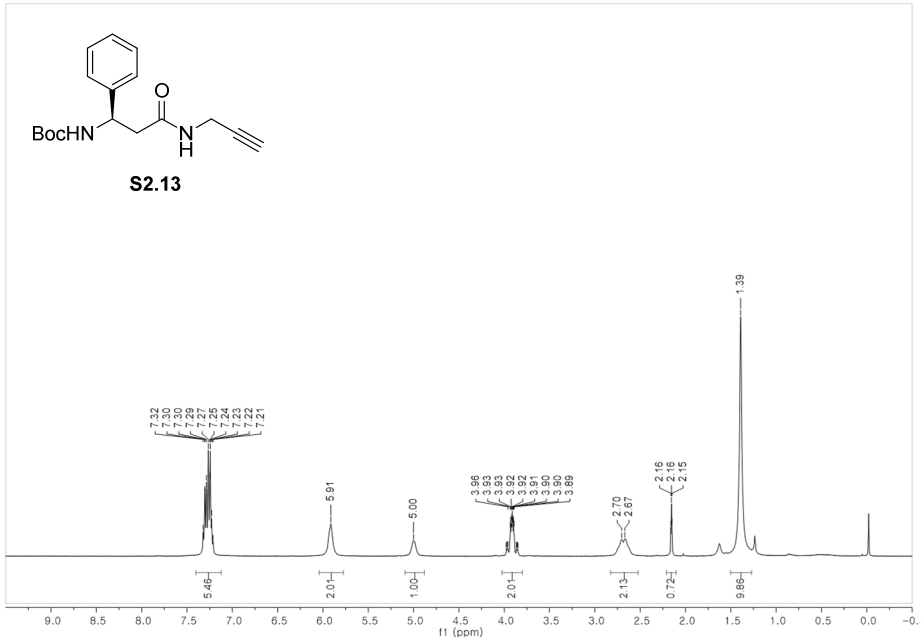

44.4
42.9
41.1
40.8
35.2
29.5
28.6
28.7
25.9
77.5
77.2
76.9
128.7
128.3
128.3
136.8
156.7
155.7
170.1
f1 (ppm)

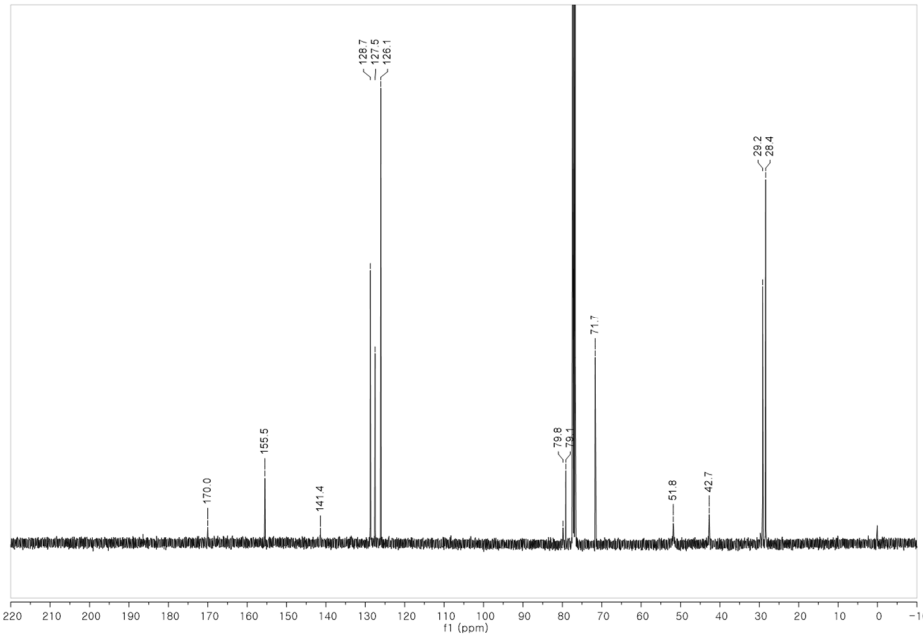

BocHN
O
N
H
S2.11
1.41
7.30
7.28
7.26
7.24
7.23
7.21
5.89
5.36
4.84
4.82
4.81
4.79
4.79
4.12
4.09
4.08
4.06
3.00
2.97
2.85
2.80
2.78
2.75
2.46
2.44
2.41
2.39
2.29
2.29
2.27
2.24
2.22
6.69
0.86
0.84
0.96
1.08
1.00
1.04
1.06
1.97
10.50
f1 (ppm)


169.8
155.6
138.0
129.4
128.6
126.6
84.0
70.5
49.5
40.5
39.2
36.8
28.4
22.1
f1 (ppm)

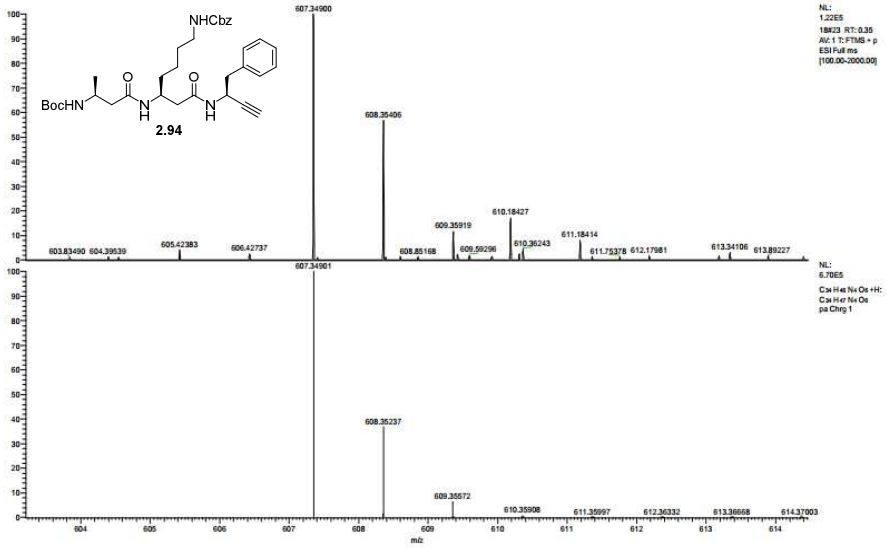

BocHN
O
N
H
S2.12
1.43
7.26
6.24
4.97
4.66
4.64
4.63
4.62
3.66
2.49
2.46
2.43
2.41
2.37
2.24
2.24
2.24
2.23
1.94
1.90
1.89
1.87
1.86
1.84
1.82
1.01
1.00
0.99
0.99
0.98
0.98
0.98
0.97
0.97
0.94
0.93
0.92
0.92
0.91
-0.00
1.00
1.04
1.14
1.19
2.09
0.85
2.25
5.75
5.76
f1 (ppm)

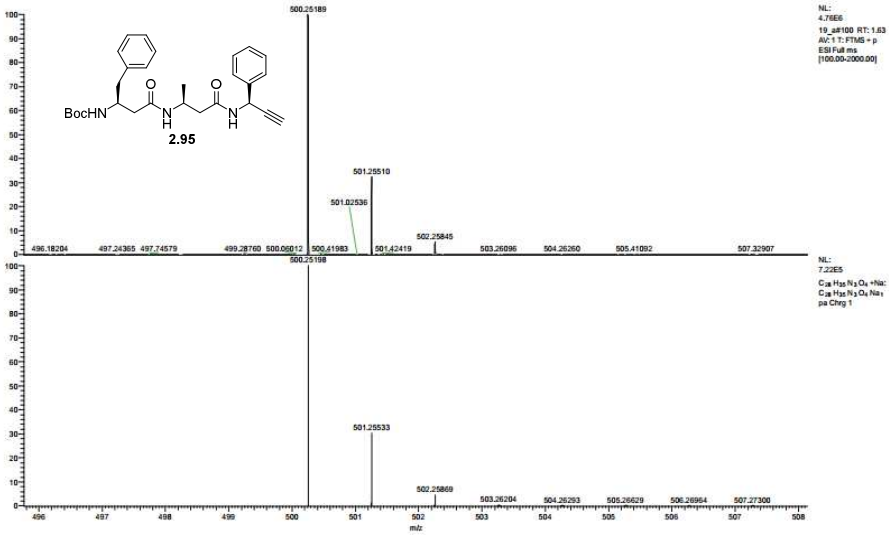

81.7
77.4
77.1
76.7
71.8
32.5
28.4
47.1
39.5
53.5
19.4
18.9
18.4
17.7
170.1
156.1
f1 (ppm)

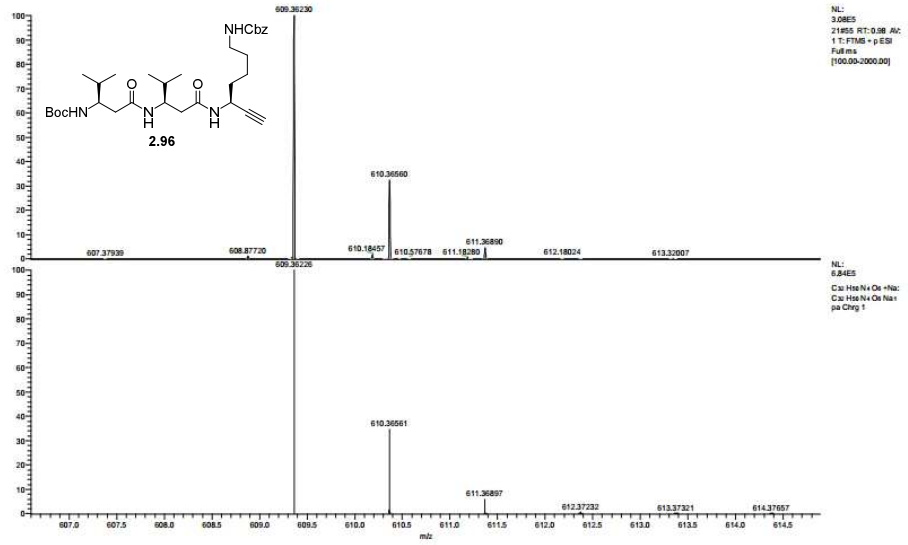

BocHN
O
N
H
S2.13
7.32
7.30
7.30
7.29
7.27
7.25
7.24
7.23
7.22
7.21
5.91
5.00
3.96
3.93
3.93
3.92
3.92
3.91
3.90
3.90
3.89
2.70
2.67
2.16
2.16
2.15
1.39
5.46
2.01
1.00
2.01
2.13
0.72
9.86
f1 (ppm)

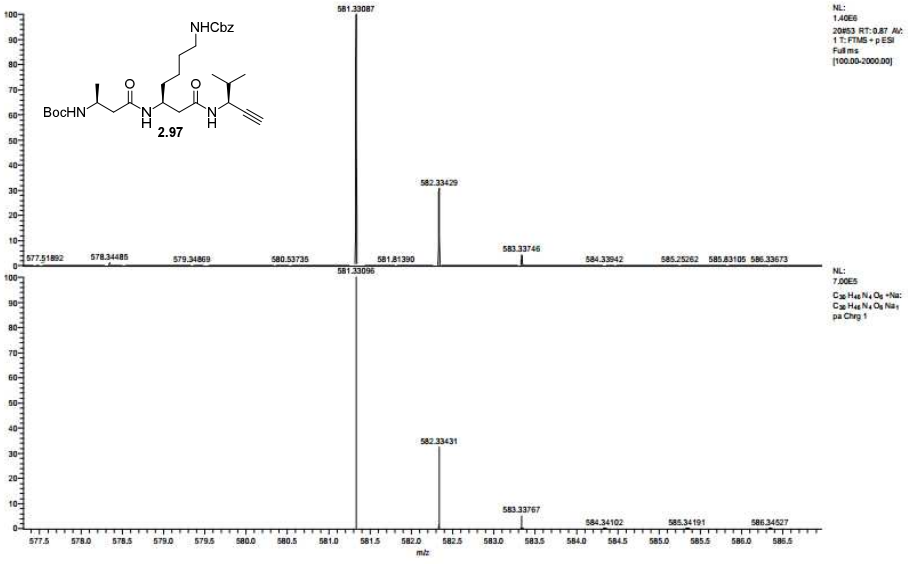

128.7
127.5
126.1
79.8
79.1
71.7
155.5
170.0
141.4
51.8
42.7
29.2
28.4
f1 (ppm)

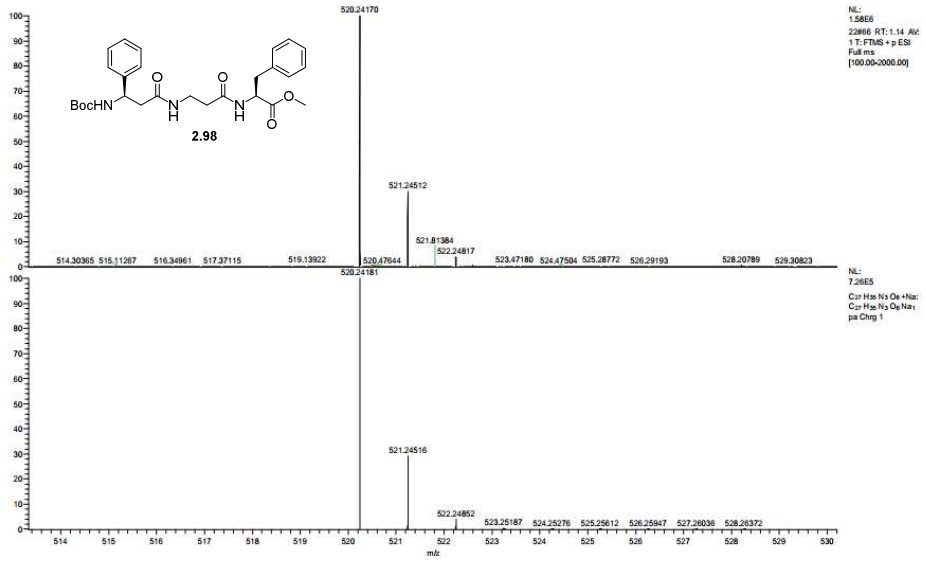
Mass Spectra for Tripeptides

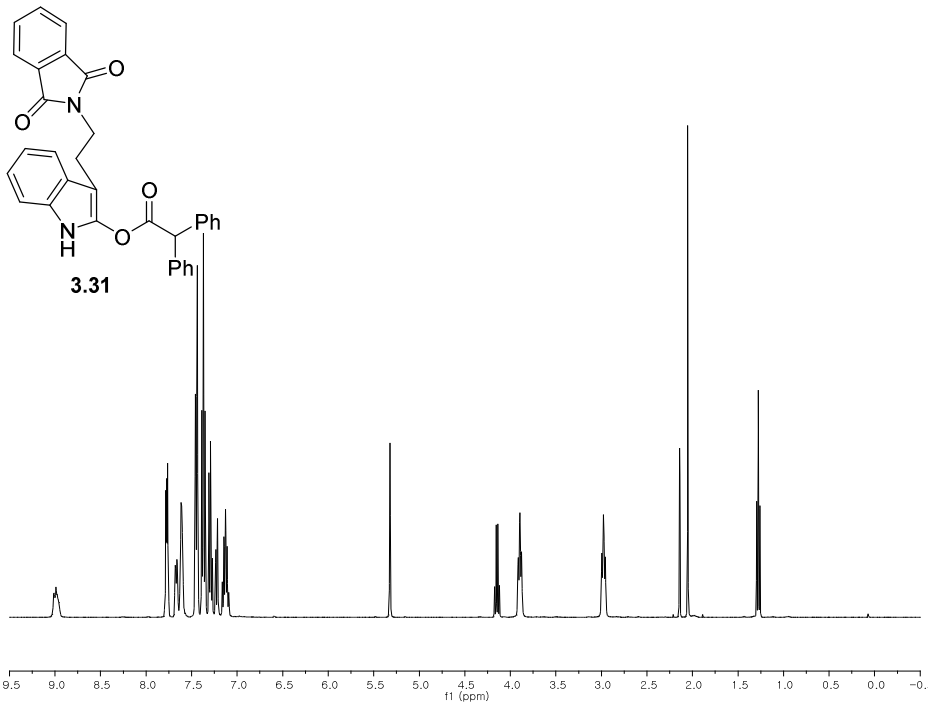


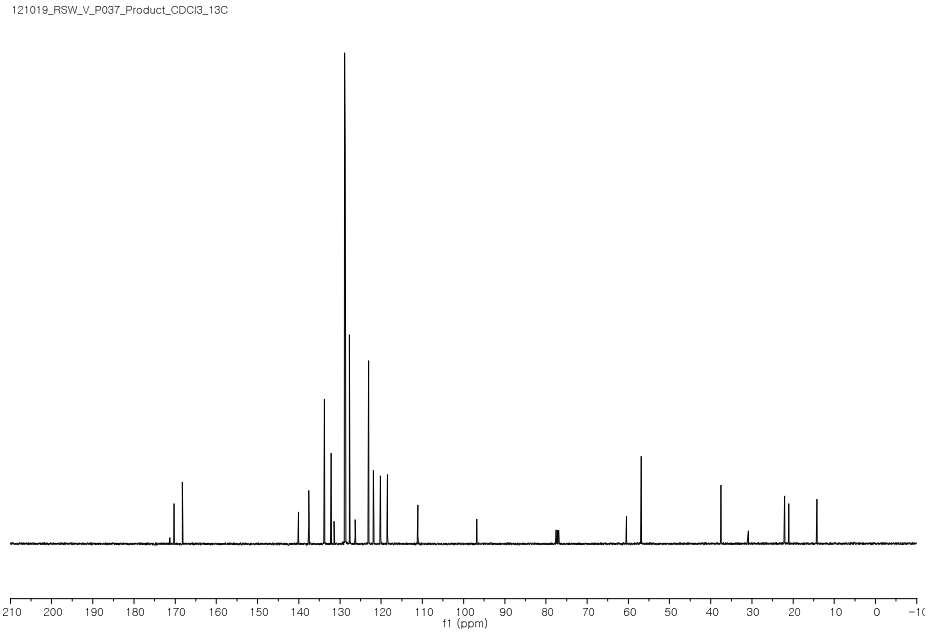


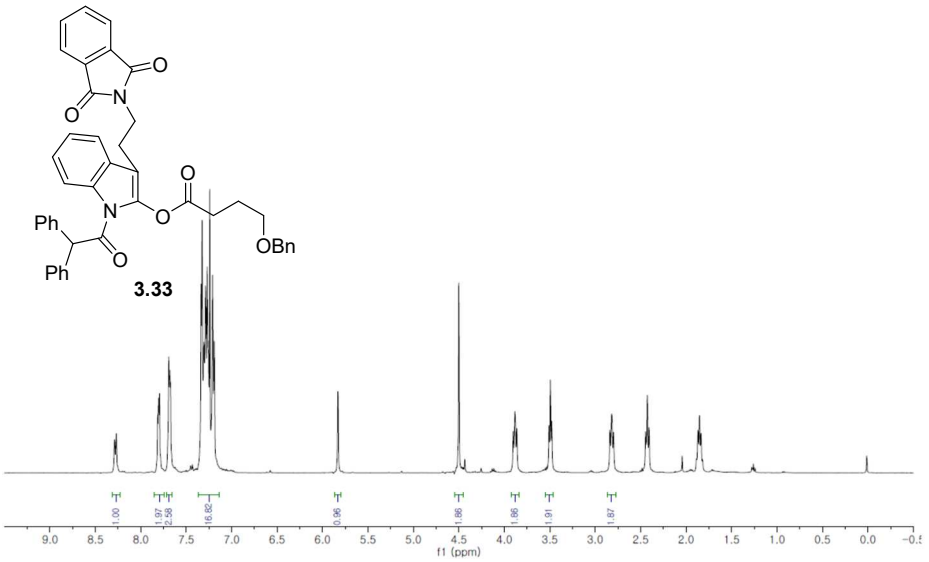

NHCbz
BocHN
2.96
609.36230
610.36560
611.36890
607.37939
608.87720
610.18457
610.57678
611.18280
612.18024
613.32807
609.36226
610.36561
611.36897
612.37232
613.37321
614.37657
m/z

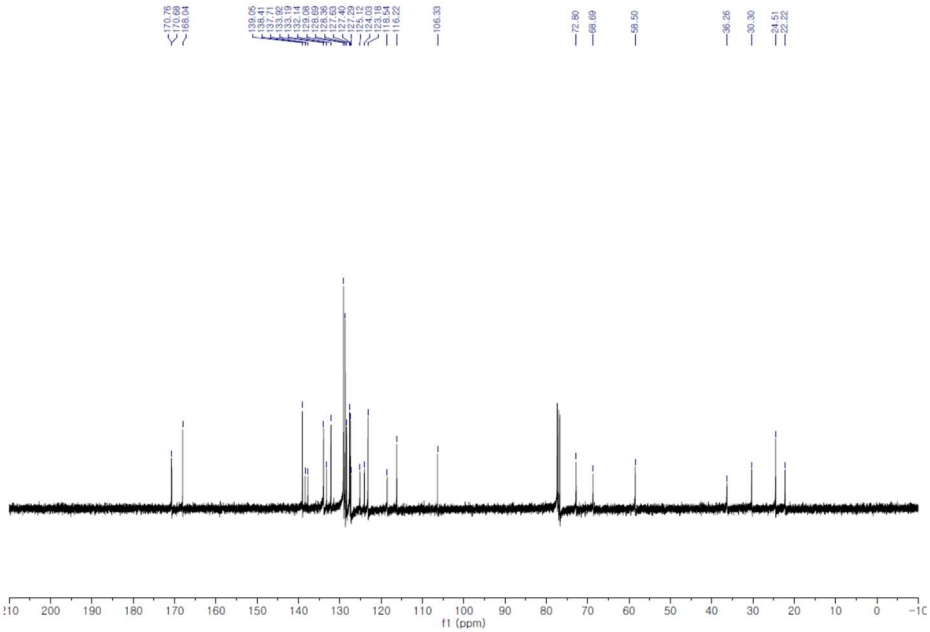

NHCbz
BocHN
2.97
581.33087
582.33429
583.33746
577.51892
578.34485
579.34869
580.53735
581.81390
584.33942
585.25262
585.83105
586.33673
581.33096
582.33431
583.33767
584.34102
585.34191
586.34527
m/z

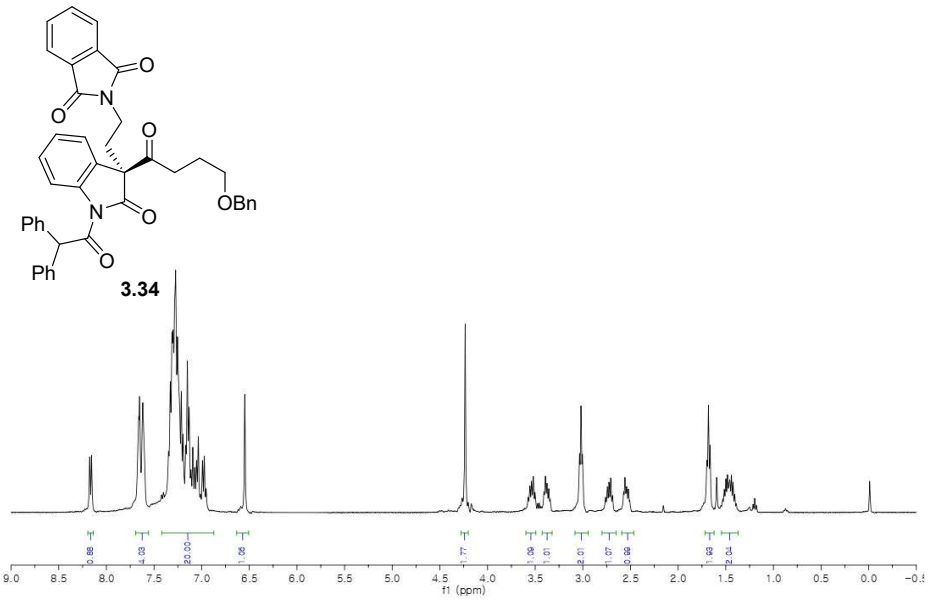

BocHN
2.98
520.24170
521.24512
521.81384
522.24817
514.30365
515.11267
516.34961
517.37115
519.13922
520.47644
523.47180
524.47504
525.28772
526.29193
528.20789
529.30823
NL:
1.58E6
22#66 RT: 1.14 AV:
1 T: FTMS + p ESI
Full ms
[100.00-2000.00]
526.24181
521.24516
522.24852
523.25187
524.25276
525.25612
526.25947
527.26036
528.26372
NL:
7.26E5
m/z

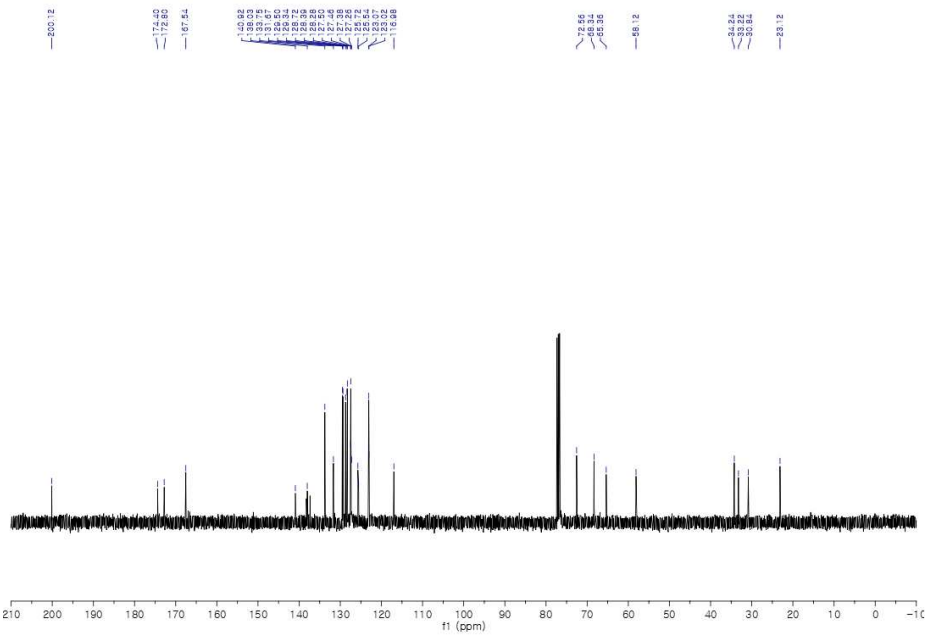

O
O
N
O
N
H
O
O
Ph
Ph
3.31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

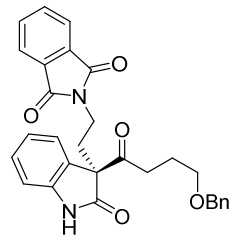

121019_RSW_V_P037_Product_CDCl3_13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
N
O
N
O
O
Ph
Ph
O
OBn
3.33
1.00
1.97
2.58
16.82
0.96
1.86
1.86
1.91
1.87
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

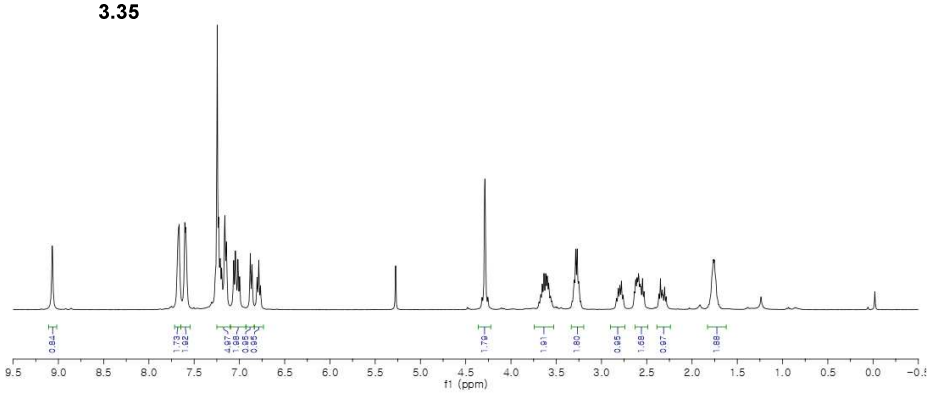

170.76
170.68
168.04
139.05
138.41
137.71
133.19
132.14
129.46
128.69
128.36
127.93
127.40
125.12
124.03
123.15
118.54
116.22
106.33
72.80
68.69
58.50
36.26
30.30
24.51
22.22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

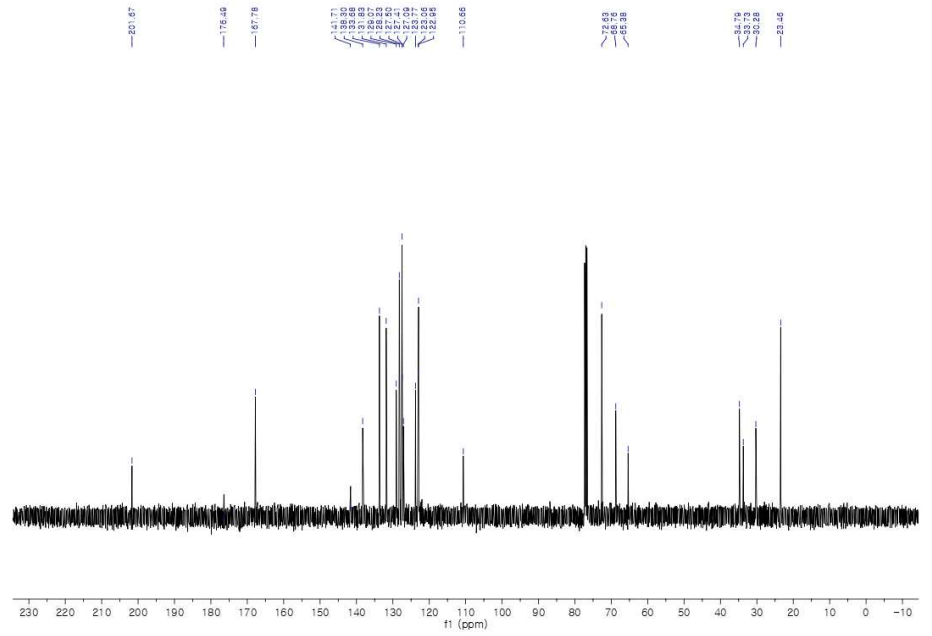

O
O
N
O
O
OBn
N
O
Ph
Ph
O
3.34
f1 (ppm)


f1 (ppm)

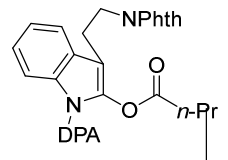

O
N
O
O
N
H
O
OBn

3.35

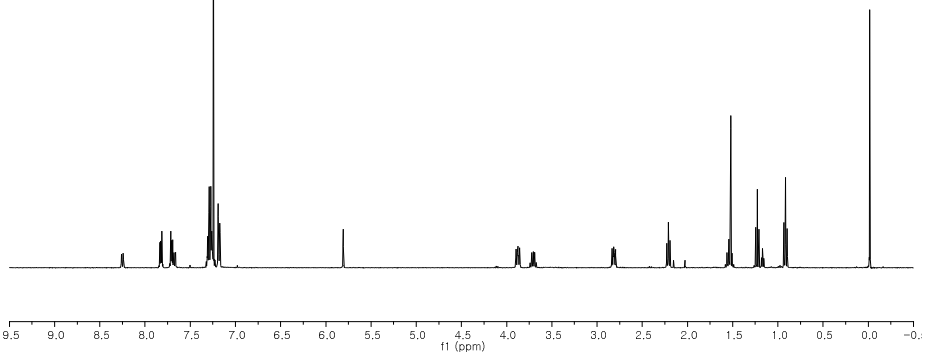

0.84
1.73
1.82
4.67
4.68
4.85
4.85
1.79
1.91
1.80
0.95
1.68
0.97
1.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


201.67
176.49
167.78
141.71
138.30
138.08
131.89
128.83
128.57
128.50
127.93
127.49
123.37
122.95
122.45
110.66
78.83
68.76
66.98
34.79
33.73
33.28
23.46
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

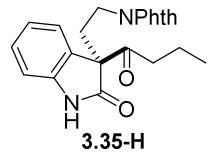
121020_RSW_V_P038_recrystallization_from_EtOH_CDCl3_1H



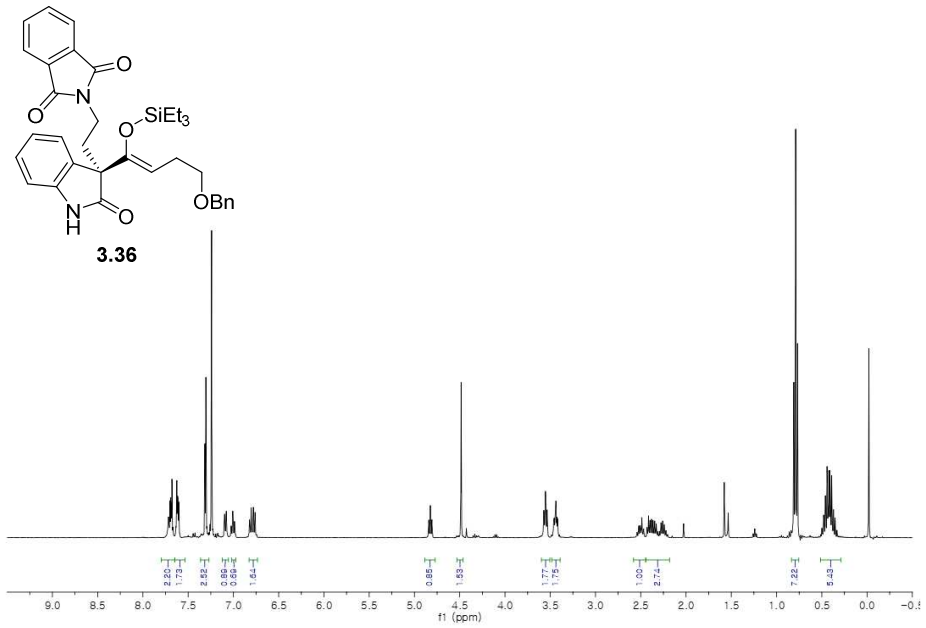
S3.1

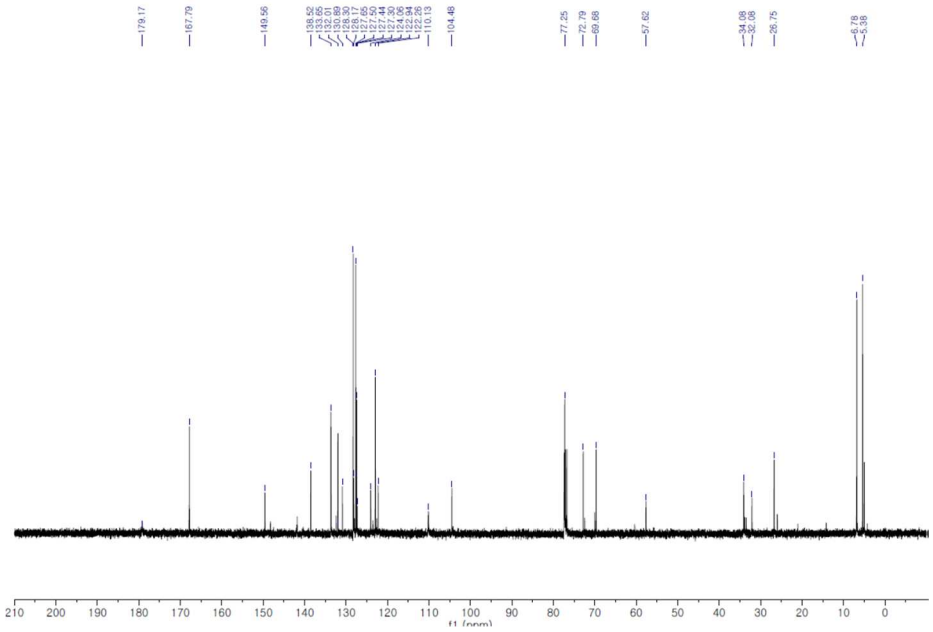


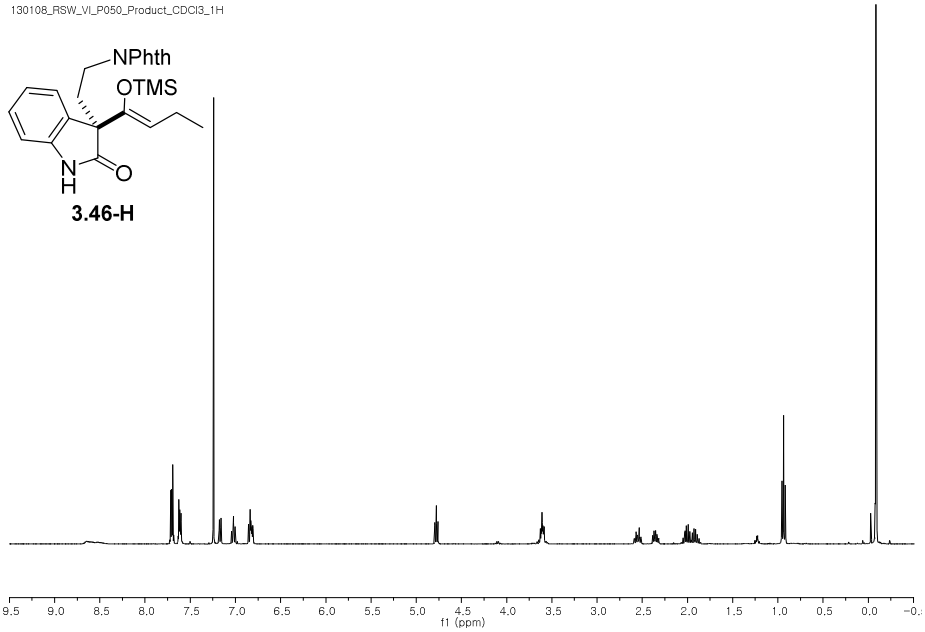
121226_RSW_VI_P040_Product_CDCl3_1H
121226_RSW_VI_P040_Product
CDCl3_1H

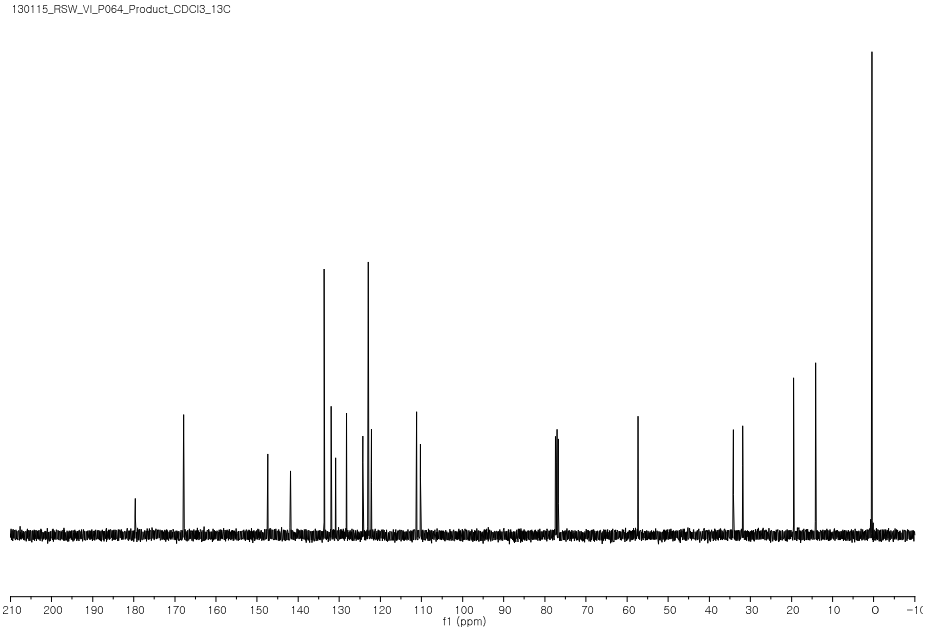


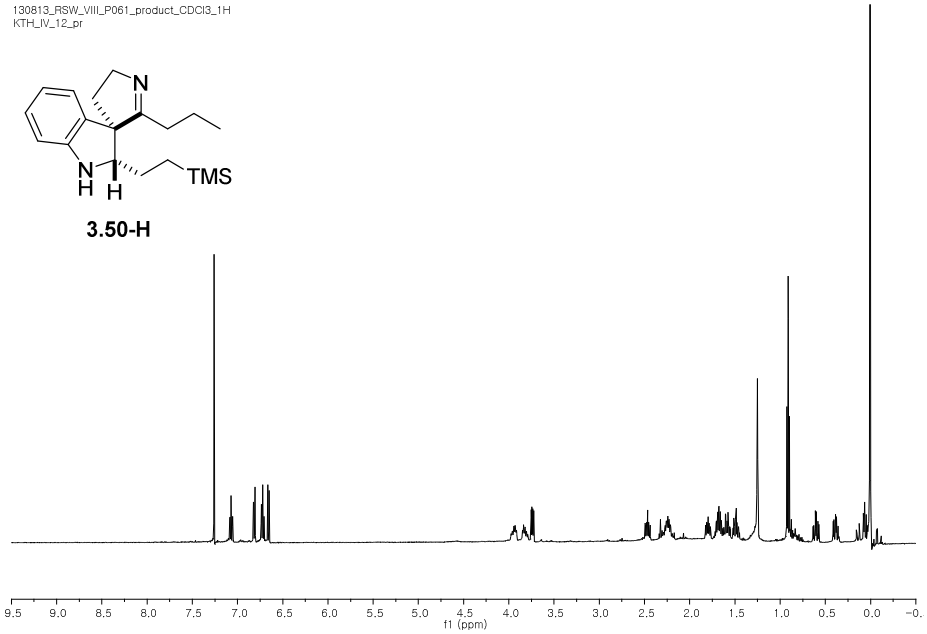
3.35-H

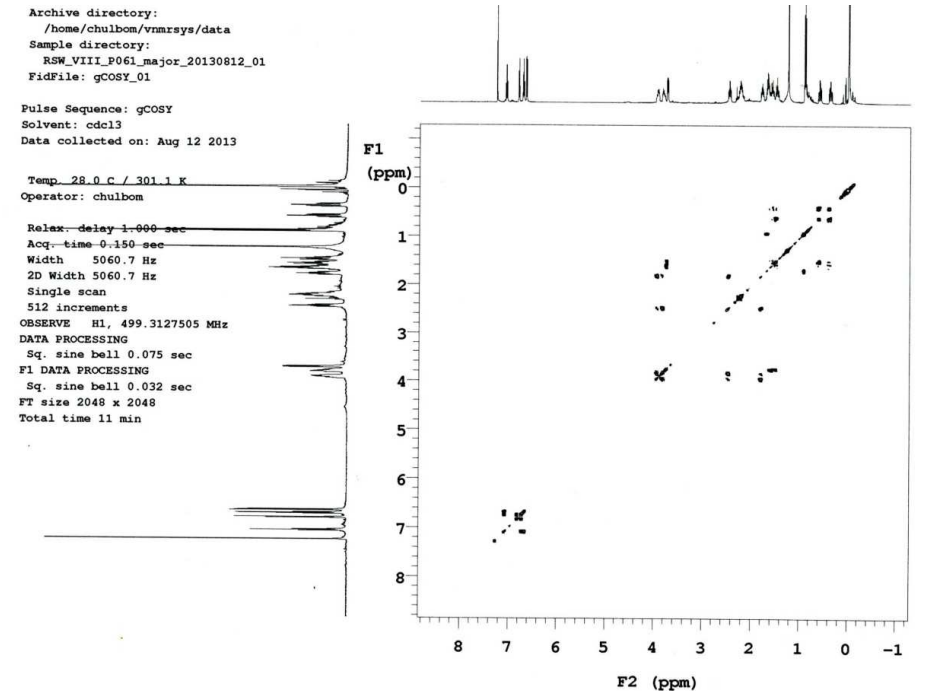

O
N
O
SiEt3
O
OBn
N
H
O
3.36
2.23
1.73
2.52
0.65
0.66
1.64
0.65
1.53
1.77
1.75
1.00
2.74
7.22
5.43
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

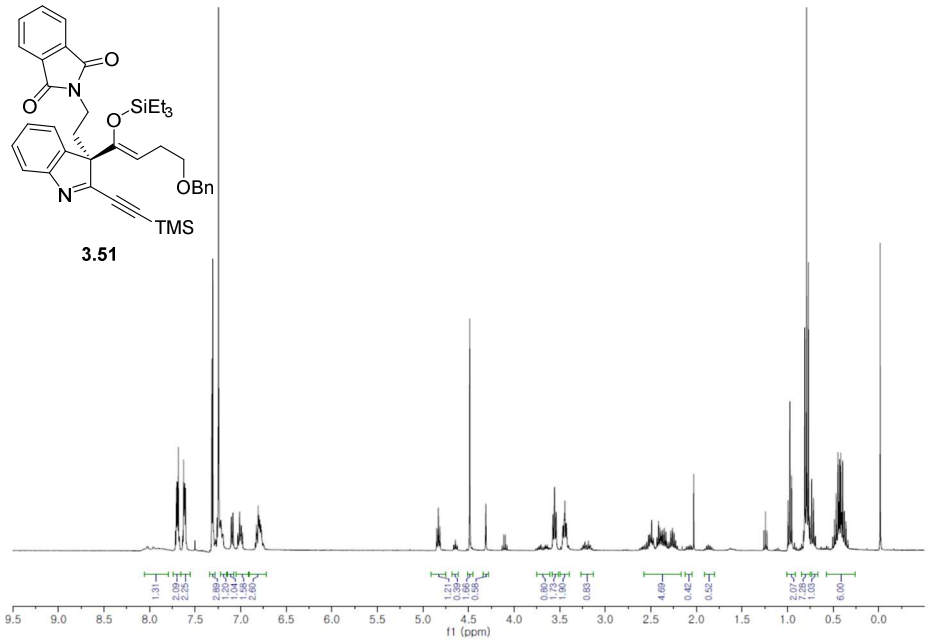

179.17
167.79
149.56
138.52
133.65
132.01
130.68
128.30
127.50
127.30
124.06
123.84
122.29
110.13
104.48
77.25
72.79
69.68
57.62
34.08
32.08
26.75
8.78
5.38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

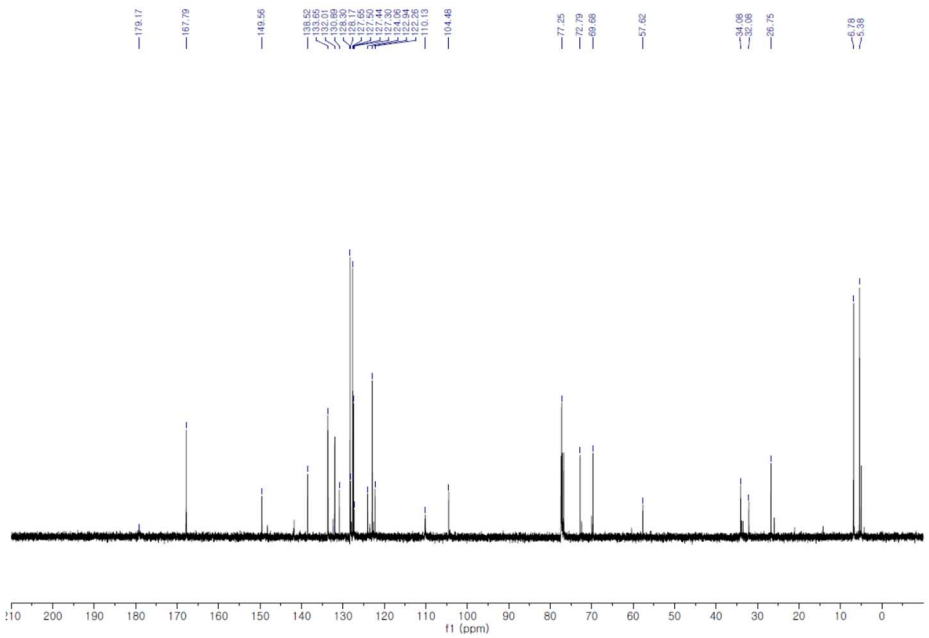

130108_RSW_VI_P050_Product_CDCl3_1H
NPhth
OTMS
N
H
O
3.46-H
f1 (ppm)

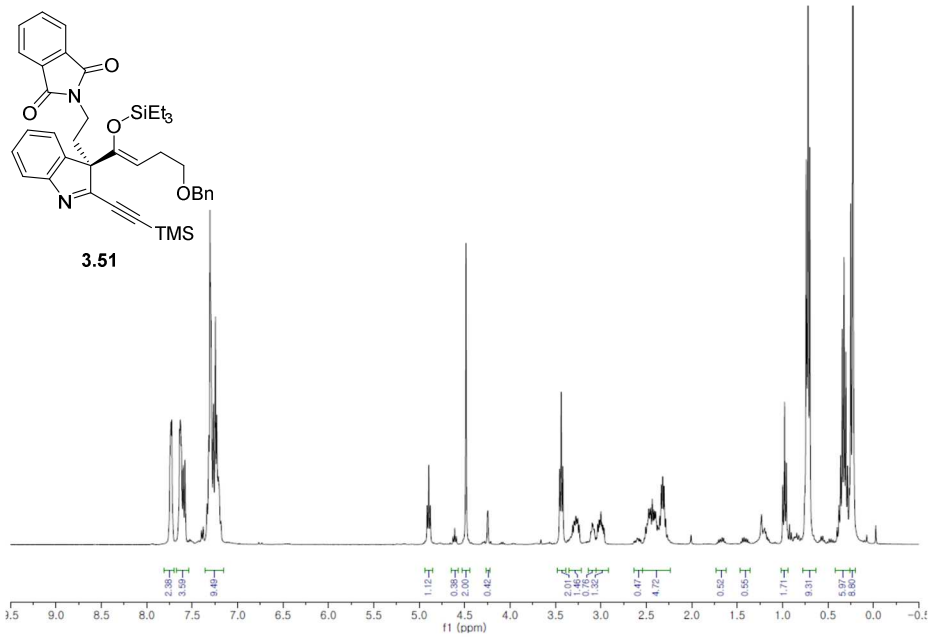

130115_RSW_VI_P064_Product_CDCl3_13C
f1 (ppm)

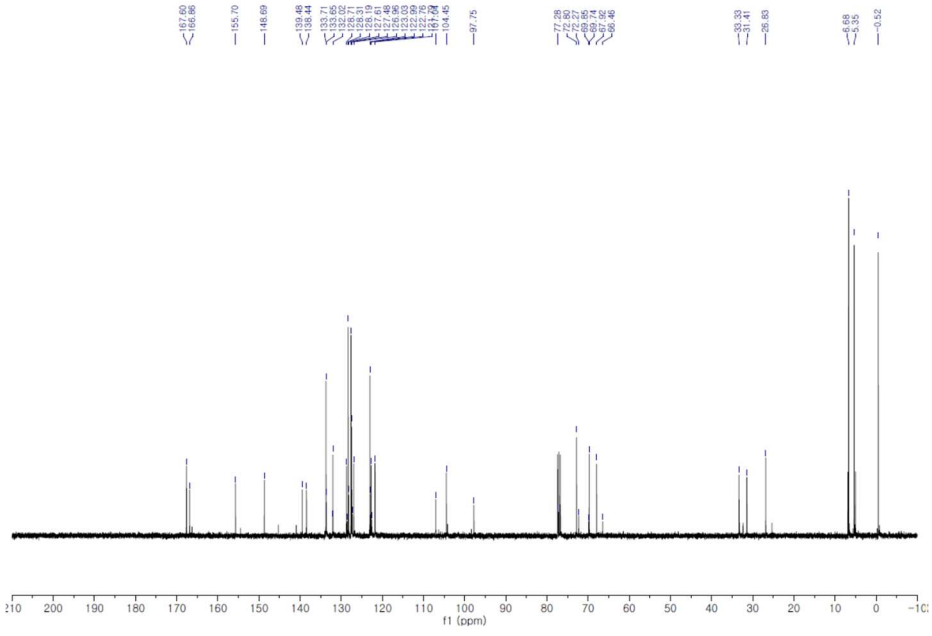

130813_RSW_VIII_P061_product_CDCl3_1H
KTH_IV_12_pr
N
N
H
H
TMS
3.50-H
f1 (ppm)

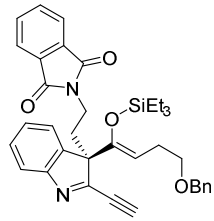

Archive directory:
/home/chulbom/vnmrsys/data
Sample directory:
RSW_VIII_P061_major_20130812_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Aug 12 2013
Temp. 28.0 C / 301.1 K
Operator: chulbom
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 5060.7 Hz
2D Width 5060.7 Hz
Single scan
512 increments
OBSERVE H1, 499.3127505 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.032 sec
FT size 2048 x 2048
Total time 11 min
F1 (ppm)
F2 (ppm)


O
O
N
O
SiEt3
OBn
N
TMS
3.51
1.31
2.09
2.25
2.88
2.00
1.04
1.58
2.60
1.21
0.39
0.46
0.58
0.86
1.73
1.90
0.83
4.69
0.42
0.52
2.07
1.76
1.05
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

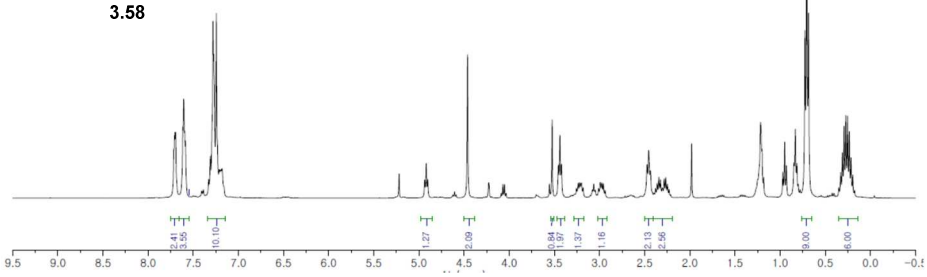

179.17
167.79
149.56
138.52
133.65
131.01
130.89
128.30
127.77
127.65
127.54
127.44
127.30
125.44
125.05
122.94
122.26
110.13
104.48
77.25
72.79
69.68
57.62
34.08
32.06
26.75
6.79
5.38
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
N
O
SiEt3
OBn
N
TMS
3.51
f1 (ppm)

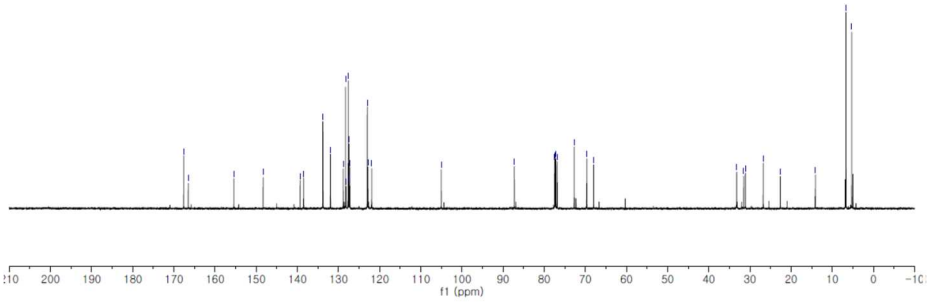

f1 (ppm)

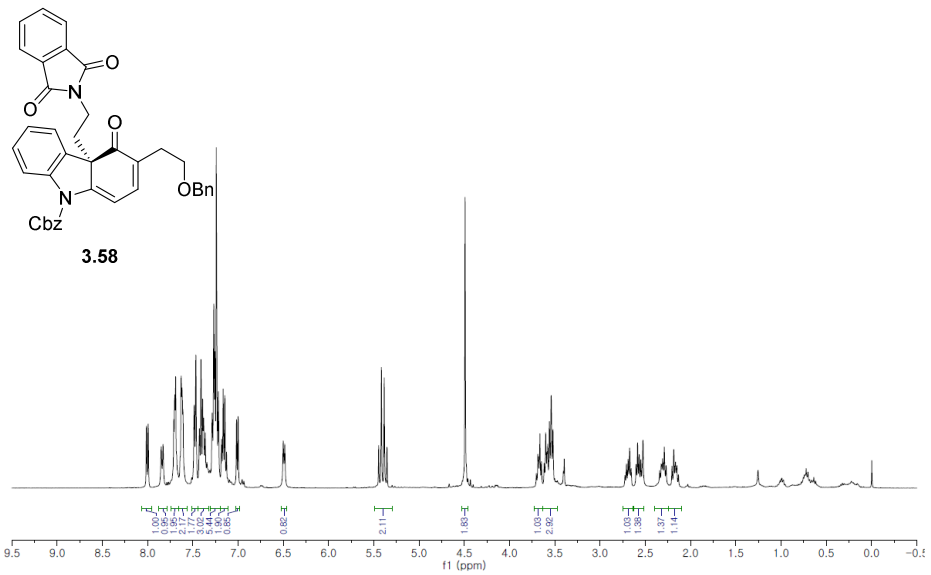

O
O
N
O
SiEt3
OBn
N

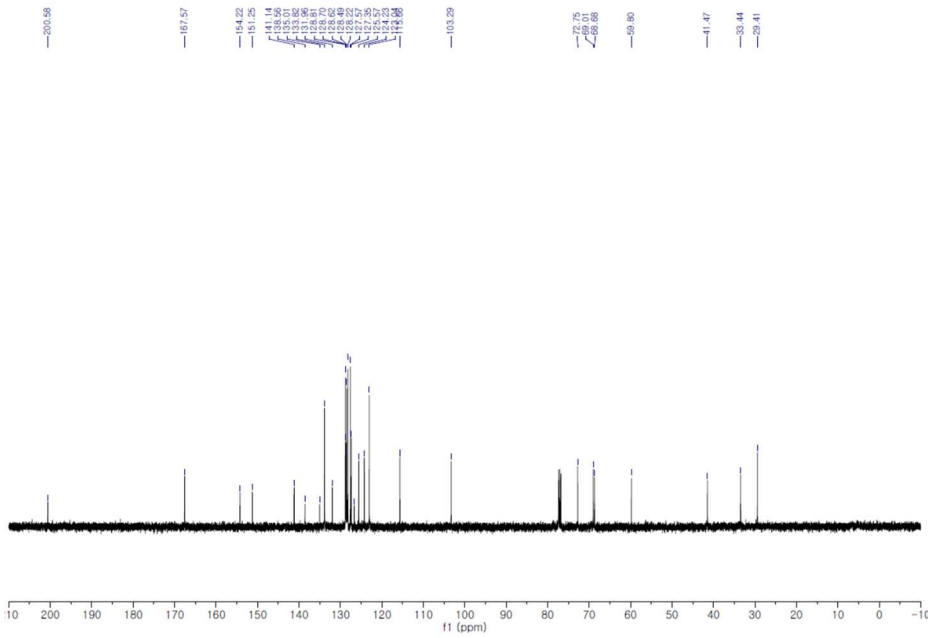
3.58

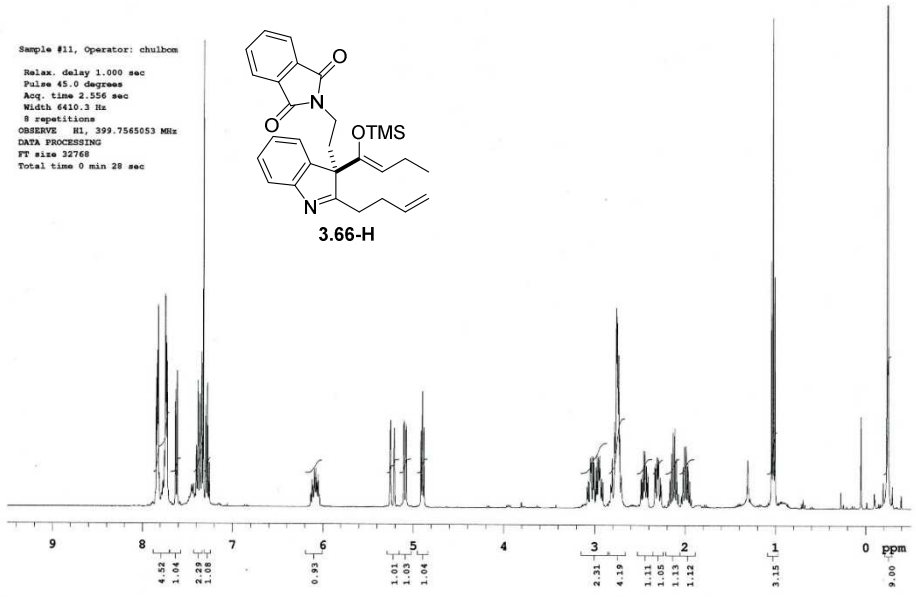

2.41
3.55
10.10
1.27
2.09
0.84
1.97
1.37
1.16
2.13
2.56
9.00
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

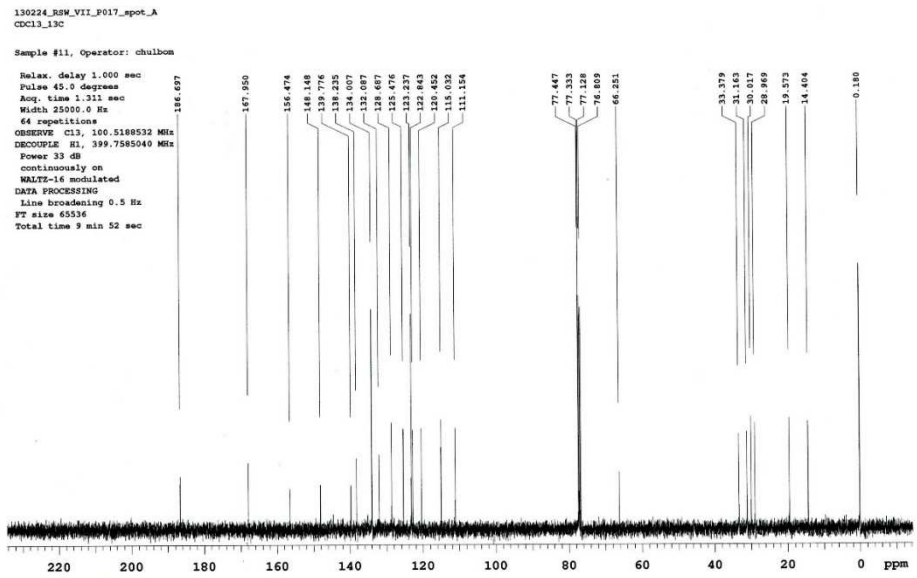

167.63
166.51
155.43
148.32
139.92
138.47
133.79
131.93
128.83
128.77
128.15
127.99
127.48
127.44
127.22
123.01
122.69
121.91
105.02
87.24
77.48
77.36
72.16
71.84
70.72
69.64
67.99
33.23
31.53
31.12
29.78
29.60
14.09
8.66
8.59

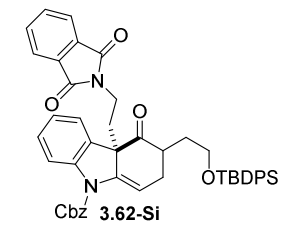

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
N
O
OBn
N
Cbz
3.58
f1 (ppm)


200.58
167.57
154.22
151.25
141.14
138.56
135.01
131.96
103.29
72.75
69.01
68.68
59.80
41.47
33.44
29.41
f1 (ppm)

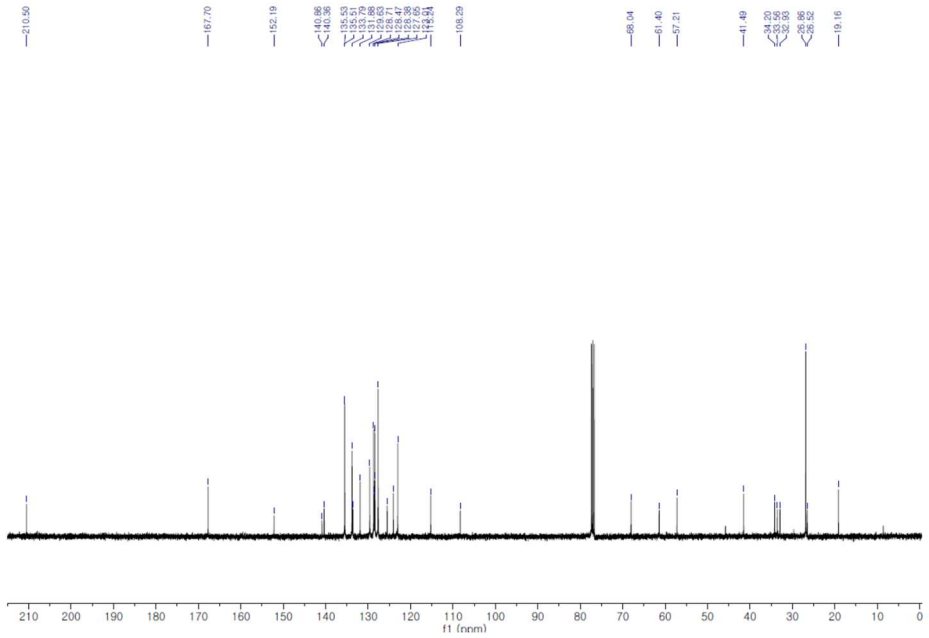

Sample #11, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
N
O
OTMS
N
3.66-H
9
8
7
6
5
4
3
2
1
0 ppm
4.52
1.04
2.28
1.08
0.93
1.01
1.03
1.04
2.31
4.19
1.11
1.05
1.13
1.12
3.15
9.00

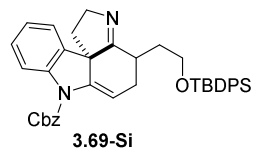

130224_RSW_VII_P017_spot_A
CDCl3_13C
Sample #11, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.5188532 MHz
DECOUPLE H1, 399.7585040 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 52 sec
186.697
167.950
156.474
148.148
139.776
138.235
134.007
132.087
128.687
125.476
123.237
122.843
120.452
118.032
111.154
77.447
77.333
77.128
76.809
66.251
33.379
31.163
30.017
28.969
19.573
14.404
0.180
220
200
180
160
140
120
100
80
60
40
20
0 ppm


O
N
O
O
OTBDPS
N
Cbz

3.62-Si

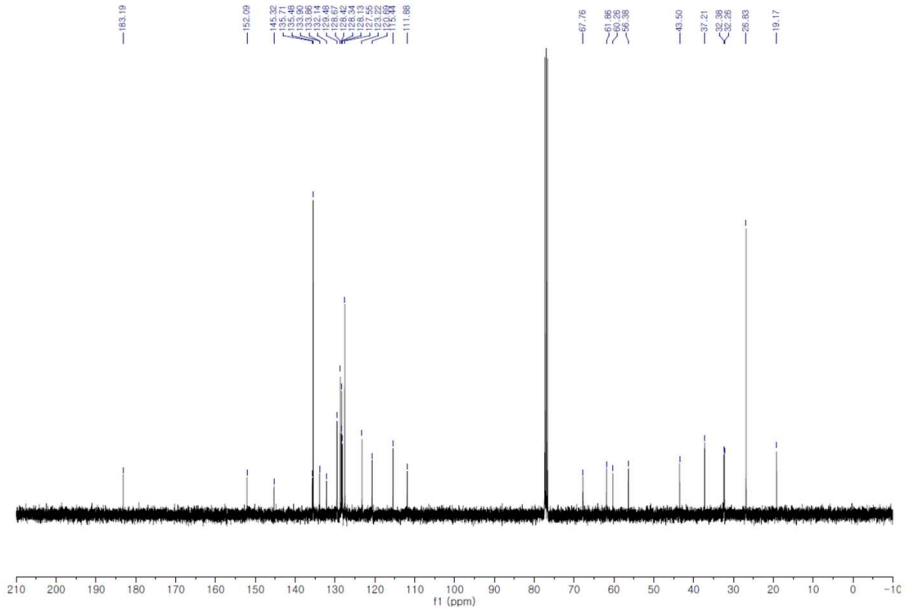
1.46
1.77
4.67
1.88
7.68
0.04
0.84
0.80
1.00
0.89
2.00
1.13
1.08
1.02
3.51
1.34
1.10
7.43
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0
f1 (ppm)

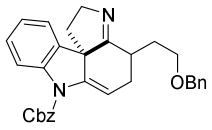

210.50
167.70
152.19
140.86
140.36
135.53
135.51
133.79
131.88
129.63
128.71
128.47
128.38
127.65
125.24
108.29
68.04
61.40
57.21
41.49
34.20
33.56
33.38
26.86
26.82
19.16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N
OTBDPS
N
Cbz

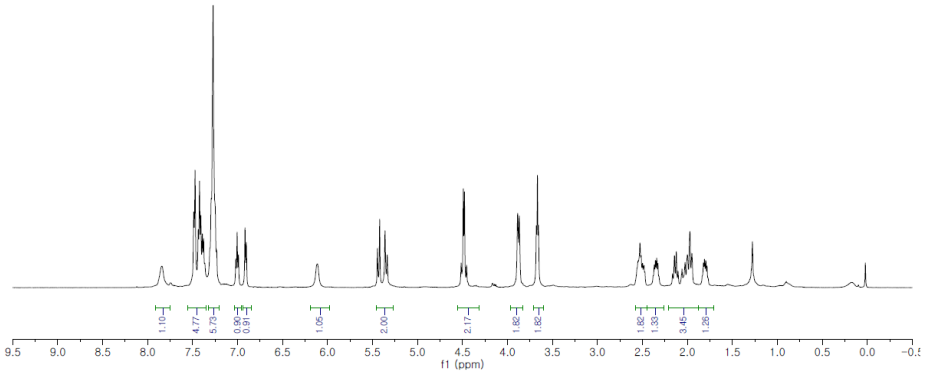
3.69-Si

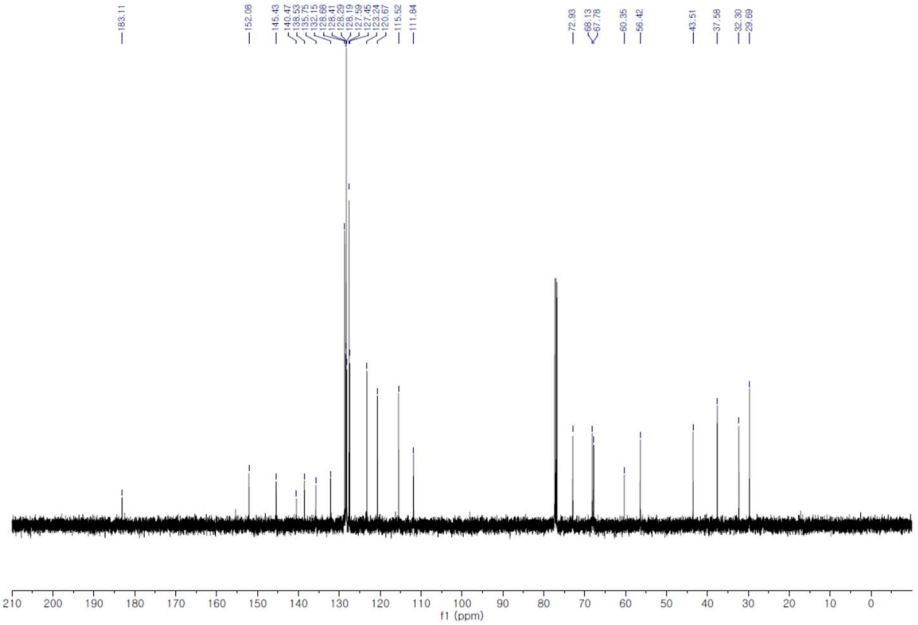
0.87
3.43
1.05
10.11
1.05
0.94
0.99
2.00
4.23
2.35
1.32
1.34
2.03
2.27
9.50
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

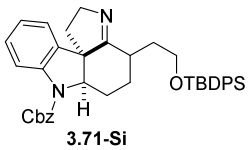

163.19
152.09
145.32
145.71
135.46
133.90
133.60
132.14
129.49
128.87
128.42
128.34
128.13
127.95
123.22
121.64
120.94
111.86
67.76
61.86
60.25
56.38
43.50
37.21
30.98
30.29
26.83
19.17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N
OBn
N
Cbz

S3.4

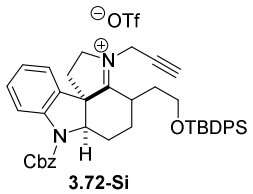

1.10
4.77
5.73
0.96
0.91
1.05
2.00
2.17
1.82
1.82
1.82
1.33
3.45
1.28
f1 (ppm)


183.11
152.08
145.43
140.47
138.53
135.70
132.15
129.66
128.41
128.29
128.19
127.59
127.45
124.54
120.67
115.52
111.84
72.93
68.13
67.78
60.35
56.42
43.51
37.98
32.30
29.69
f1 (ppm)


N
OTBDPS
N
H
Cbz

3.71-Si

1.00
5.18
14.79
1.79
0.86
3.54
1.81
3.29
2.60
3.23
3.49
3.00
6.02
3.85
14.26
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OTf
N
N
H
Cbz
OTBDPS

3.72-Si

1.14
3.54
9.27
0.99
0.95
2.82
1.01
1.00
0.87
2.00
0.90
1.98
1.77
3.12
4.57
8.80
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)